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THE EFFECT OF EXPERIMENTAL HYPERTHYROIDISM AND OF INANITION ON THE HEART, LIVER AND KIDNEYS*

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The literature on the effects of inanition was reviewed by Morgulis [1] in 1923 and by Jackson [2] in 1925. As our paper was being prepared, Jackson's more recent review of the subject appeared.[3] The effect of starvation on the body as a whole and on individual organs is fairly well established, in spite of certain contradictory reports. The feeding of thyroid has been shown to cause loss of body weight by Magnus-Levy,[4] Farranti,[5] Hewitt,[6] Kuriyama [7] and others. But, as pointed out by Kunde,[8] the effect of thyroid feeding on the body weight of dogs varies within wide limits. In our series of dogs, three animals were of approximately the same initial body weight, namely, from 11.6 to 11.9 Kg. Each received 10 Gm. of desiccated thyroid daily and all were kept on the same diet. One lost only 14.3 per cent of its body weight after forty-eight days of thyroid feeding; another 24.2 per cent after fifty-seven days, and the third 33.5 per cent after only thirty-two days (table 5 may be seen here).

Studies have been made of the weights of different organs in experimental hyperthyroidism, but apparently only in rats, mice and rabbits.

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1. Morgulis, S.: Hunger und Unterernährung, Berlin, Julius Springer, 1923.
2. Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Company, 1925.
3. Jackson, C. M.: Recent Work on the Effects of Inanition and of Malnutrition on Growth and Structure, Arch. Path. **7**:1042 (June) 1929.
4. Magnus-Levy, A.: Berl. klin. Wchnschr. **32**:650, 1895.
5. Farranti, R.: Brit. M. J. **11**:1363, 1913.
6. Hewitt, J. A.: Quart. J. Exper. Physiol. **8**:113, 1915.
7. Kuriyama, S.: Am. J. Physiol. **43**:481, 1917.
8. Kunde, Margaret M.: Am. J. Physiol. **82**:195, 1927.

So far as we have been able to discover, no one has compared the effect of hyperthyroidism with that of inanition on the weights of different organs. This we have endeavored to do in the present paper.

The facts here presented were obtained from a study of the body weights and the heart, liver and kidney weights of thirty-one normal adult dogs and nine adult dogs each of which was fed 10 Gm. daily of dessicated thyroid (Armour & Co.), and one dog which received 20 Gm. daily, for periods ranging from thirty-two to one hundred days, all of which were kept on the same diet and under the same conditions as the normal controls. For comparison, corresponding weights have been collected from studies on inanition chiefly from Junkersdorf's laboratory.

THE EFFECT OF INANITION AND HYPERTHYROIDISM ON THE HEART

In a previous paper,[9] we presented evidence that experimental hyperthyroidism may cause a hypertrophy of the heart; that this hypertrophy is related to the loss of body weight, being most marked in those animals which had lost from 25 to 35 per cent of body weight; and that the hypertrophy affects all of the chambers of the heart, but the left ventricle slightly more than the others. Hypertrophy of the heart in experimental hyperthyroidism in rabbits or white rats has been described by Iscovesco,[10] Hoskins,[11] Herring,[12] Hewitt[13] and Cameron and Carmichael.[14] Hoskins estimated that feeding thyroid caused an increase in the size of the heart to the extent of 24.6 and 16.7 per cent in old and young female rats, respectively, and 36 and 15.4 per cent in corresponding males. Herring concluded that "the increase in weight of the heart in thyroid fed (0.2 Gm. daily) male rats averaged 123 per cent, and in thyroid fed females, 59 per cent." "In both male and female rats the heaviest hearts were in the animals which received most thyroid."

Jackson[2] cited the opinion of Lucas that the heart weight in starved dogs and rabbits is apparently normal; of Collard and Martigny, that the heart becomes atrophic in inanition; and of Kusmin, that a functional hypertrophy of the heart occurs in starvation with hyperthermia. E. Voit[15] concluded that the heart may lose 16 per cent of its original

9. Simonds, J. P., and Brandes, W. W.: The Size of the Heart in Experimental Hyperthyroidism, Arch. Int. Med., to be published.
10. Iscovesco, H.: Compt. rend. Soc. de biol. **76**:75, 1914.
11. Hoskins, E. R.: J. Exper. Zool. **21**:295, 1916.
12. Herring, P. T.: Quart. J. Exper. Physiol. **11**:231, 1917.
13. Hewitt, J. A.: Quart. J. Exper. Physiol. **12**:347, 1918-1920.
14. Cameron, A. T., and Carmichael, J.: J. Biol. Chem. **45**:69, 1920.
15. Voit, E.: Ztschr. Biol. **46**:195, 1905.

weight in starvation. C. Voit,[16] however, compared that in starvation the heart suffers no loss of weight. Krieger[17] compared the heart weight and body weight in 123 emaciated persons and thought that the loss of heart weight was slightly less than that of the body weight in malnutrition from various causes. His estimates of the loss of body weight and of heart and liver weight are shown in table 1. In Krieger's cases, the estimated loss of heart weight was in all instances less (average, 9 per cent; minimum, 3.4 per cent; maximum, 17.5 per cent) than the estimated loss of body weight. They were more nearly equal in chronic diarrhea, in which dehydration was probably a factor of importance. Levine[18] believed that the heart was more or less involved in every type of malnutrition and that malnutrition is, therefore, a pathogenic factor of prime importance in various cardiovascular disorders.

Witsch[19] starved three dogs until they lost from 49 to 60 per cent of their original body weight, and compared the ratio of heart weight

TABLE 1.—*Krieger's Estimates of the Loss of Body Weight, Loss of Heart Weight and Loss of Liver Weight Through Malnutrition from Various Causes*

Pathologic Condition	Loss of Body Weight, per Cent	Loss of Liver Weight, per Cent	Loss of Heart Weight, per Cent
Insanity	38.7	32.1	34.8
Chronic diarrhea	48.4	43.5	45.0
Malignant tumors	38.0	32.8	33.2
Chronic general infections	43.9	28.0	30.7
Tuberculosis	43.0	27.7	31.9
Old age	35.8	20.1	18.3

to final body weight in these dogs with the ratio of heart weight to body weight in eight normal dogs. She concluded that no relative loss of heart weight occurred in inanition; but that an absolute loss of 42, 26.3 and 43 per cent of heart weight, respectively, occurred in these three dogs. Witsch was of the opinion that the heart takes part to a high degree in the atrophy of general inanition. There was an increase in the water content of the hearts of the starved dogs; hence a part of the loss of heart weight was veiled. She noted individual differences in the loss of weight of the starved dogs. One animal, starved for eighty-three days, lost 60 per cent of its body weight, but only 26.3 per cent of its heart weight.

METHOD

In our experiments, we weighed the dogs at the beginning of the feeding of thyroid and at the end of the experiment. These weights are designated, respec-

16. Voit, C.: Physiologie des allgemeine Stoffwechsels und die Ernährung, in Herrmann: Handbuch der Physiologie des Gesamtstoffwechsels, Leipzig, F. C. W. Vogel, 1881, vol. 6, p. 97.

17. Krieger, W.: Ztschr. f. ang. Anat. **7**:134, 1920.

18. Levine, V. E.: Nebraska M. J. **12**:209, 1927.

19. Witsch, Kaethe: Arch. f. d. ges. Physiol. **211**:185, 1926.

tively, original body weight (O. B. W.) and final body weight (F. B. W.). The hearts were removed immediately after death, the parietal pericardium was dissected away, the pulmonary artery and aorta were cut off at the upper level of the corresponding valves, all blood was removed, and the hearts were weighed. The subpericardial fat was then carefully dissected away, and the heart weighed again. This latter weight was the one used in our computations.

The coefficients of correlation between the weight of the fat-free heart and the original and final body weights were then computed. Similar correlation coefficients were computed for the body weights and the weights of the fat-free hearts of thirty-one normal dogs, obtained chiefly through the courtesy of Dr. A. C. Ivy from acute experiments made by a class in physiology. Correlation coefficients were computed for heart weights (probably not fat-free) and original and final body weights from data published by Witsch,[19] Junkersdorf,[20] Junkersdorf and Török[21] and Junkersdorf and Kohl,[22] in their experiments on starvation. These correlation coefficients are shown in the last column of table 2.

A correlation coefficient of 1 indicates that there is a perfect reciprocal relationship between the data compared; and the nearer the coefficient approaches 1 the closer is the correlation. From table 2 it is seen that the correlation coefficient between heart weight and final body weight in inanition is much nearer the normal than that in hyper-

TABLE 2.—*Correlation Coefficients*

Condition	Kidney Weight and Final Body Weight	Liver Weight and Final Body Weight	Heart Weight and Final Body Weight
Normal	0.9000	0.8410	0.9062
Thyrotoxicosis	0.8637	0.4620	0.8206
Inanition	0.8162	0.8001	0.9075

thyroidism; that is, the loss of heart weight in inanition more nearly corresponds to the loss of body weight than it does in hyperthyroidism. This does not, however, indicate whether there is a hypertrophy of the heart in hyperthyroidism or whether it has lost a disproportionately greater or less amount of weight than the body as a whole. In order to determine this point, the mean, minimum and maximum heart weight-body weight ratios of normal animals were compared with the corresponding heart weight-original body weight and heart weight-final body weight ratios in hyperthyroidism and inanition. These are shown together with the mean, minimum and maximum losses of body weight, in table 3.

The results shown in table 3 may be summarized as follows: 1. In the group of thyrotoxic animals in which the mean loss of body weight was 31 per cent, the mean heart weight-original body weight ratio was only slightly less (7.7 per cent) than the normal; while in a group of

20. Junkersdorf, P.: Arch. f. d. ges. Physiol. **200**:443, 1923.
21. Junkersdorf, P., and Török, P.: Arch. f. d. ges. Physiol. **211**:414, 1926.
22. Junkersdorf, P., and Kohl, A.: Arch. f. d. ges. Physiol. **211**:612, 1926.

starved animals in which the mean loss of body weight was 28.1 per cent, the mean heart weight-original body weight ratio was considerably less (22.5 per cent) than the normal. 2. The mean heart weight-final body weight ratio in hyperthyroidism was considerably greater (31.6 per cent) than normal; while the corresponding ratio in inanition was only slightly greater (7.8 per cent) than normal. 3. The minimum and maximum heart weight-original and final body weight ratios showed

TABLE 3.—*The Heart Weight-Body Weight, Liver Weight-Body Weight and Kidney Weight-Body Weight Ratios of Normal, Thyrotoxic, and Starved Dogs*

	Normal Dogs			Thyrotoxic Dogs			Starved Dogs		
Ratios*	Mean	Minimum	Maximum	Mean	Minimum	Maximum	Mean	Minimum	Maximum
H.W./O.B.W.	0.0076	0.0056	0.0098	0.0070	0.0045	0.0083	0.0059	0.0043	0.0071
H.W./F.B.W.	.....	.....	.....	0.0099	0.0092	0.0119	0.0082	0.0065	0.0090
Loss B.W.	.....	.....	.....	31.0%	14.3%	46.5%	28.1%	11.3%	49.0%
L.W./O.B.W.	0.0303	0.0183	0.0473	0.0304	0.0202	0.0364	0.0237	0.0095	0.0375
L.W./F.B.W.	....	....	....	0.0430	0.0326	0.0562	0.0298	0.0158	0.0480
Loss B.W.	....	....	....	31.0%	14.3%	46.5%	21.0%	11.3%	49.0%
K.W./O.B.W.	0.0057	0.0043	0.0081	0.0060	0.0045	0.0065	0.0040	0.0030	0.0051
K.W./F.B.W.	.....	.....	.....	0.0085	0.0069	0.0105	0.0055	0.0040	0.0077
Loss B.W.	....	....	....	31.7%	14.3%	46.5%	25.8%	10.0%	49.0%

* H.W. = heart weight; L.W. = liver weight; K.W. = kidney weight; O.B.W. = original body weight; F.B.W. = final body weight.

TABLE 4.—*The Per Cent Gain or Loss in Heart Weight in Hyperthyroidism and in Inanition*

Inanition				Thyrotoxicosis			
Percentage Loss of Body Weight	Calculated Heart Weight for Original Body Weight, Gm.	Actual Heart Weight, Gm.	Percentage Gain or Loss of Heart Weight*	Percentage Loss of Body Weight	Calculated Heart Weight for Original Body Weight, Gm.	Actual Heart Weight, Gm.	Percentage Gain or Loss of Heart Weight*
11.8	77.3	72.0	— 6.9	14.3	90.5	85.0	— 5.60
15.0	100.0	86.0	—14.0	21.7	110.0	95.0	—13.60
20.0	151.0	132.0	—12.6	24.2	87.5	92.0	+ 5.15
20.7	31.0	29.0	— 6.5	29.8	110.0	110.5	— 0.45
23.0	21.3	18.0	—15.5	30.4	73.5	80.0	+ 8.80
26.0	182.5	157.5	—13.8	33.5	90.3	89.0	— 1.45
27.0	113.5	92.0	—19.0	35.8	70.0	63.0	—10.00
29.5	69.5	49.0	—29.5	38.1	79.5	71.0	—10.70
43.5	117.0	79.0	—32.5	39.2	121.0	84.0	—30.50
49.0	151.0	87.9	—42.5	46.5	105.0	60.5	—42.50
50.15	151.5	87.0	—42.5				
Mean	105.0	79.0	—22.0		96.0	85.0	—11.00

* For the purposes of this table the per cent loss of heart weight was estimated by calculating the heart weight (normal ratio of H.W. to B.W. = 0.0076) for the original body weight and comparing this calculated heart weight with the actual heart weight.

even more marked differences than the mean ratios. This can only mean either that the heart loses proportionately less weight in hyperthyroidism than in inanition; or that there occurs an actual relative hypertrophy of the heart in hyperthyroidism.

That this difference is related to the loss of body weight is shown in table 4.

For purposes of this table the heart weight of each animal at the beginning of the experiment was calculated by multiplying the original body weight of each animal in the thyrotoxic and starved series by the mean normal heart weight-body weight ratio of 0.0076. From this table the following facts are seen: 1. In every instance in the inanition series, the actual heart weight was less than the calculated weight; while in four of the thyrotoxic dogs, the actual heart weight was either distinctly greater or less than 1.5 per cent less than the calculated weight. These four animals had lost between 25 and 35 per cent of their body weight. 2. When the loss of body weight in hyperthyroidism reaches approximately 40 per cent or more, the loss of heart weight becomes roughly proportional to that in inanition. 3. In the starved dogs, the mean loss of heart weight was 22 per cent, or approximately 6 per cent less than the mean loss of body weight; while in hyperthyroidism, the mean loss of heart weight was only 11 per cent, or 20.5 per cent less than the mean loss of body weight.

All of the aforementioned facts seem to indicate that in experimental hyperthyroidism a relative, if not an actual, hypertrophy of the heart occurs in animals that have lost from 25 to 35 per cent of their body weight. The mechanism of this hypertrophy is not easily explained. Eyster [23] insisted that hypertrophy of the heart results from tissue injury. Although injury to the myocardium has been repeatedly demonstrated in both experimental and spontaneous hyperthyroidism (literature reviewed by Goodpasture [24]), this does not appear to us to be a satisfactory explanation, chiefly because the response to tissue injury is an increase in the number of cells rather than in the size of the component cells. In cardiac hypertrophy, as has been shown by Karsner, Saphir and Todd,[25] there is an increase in the size of the heart muscle fibers without increase in their number. The theory, apparently originated by Corvisart and advocated by Cohnheim,[26] that increased work causes hypertrophy of the heart may apply in hyperthyroidism, but it does not explain the phenomenon. For it was shown by Wright [27] that in exophthalmic goiter the volume at each stroke averaged 116 cc. as compared with the normal 70 to 120 cc. at rest, and the output per minute averaged 11.7, as compared with the normal 5 to 8 liters at

23. Eyster, J. E. A.: Experimental and Clinical Studies in Cardiac Hypertrophy, J. A. M. A. **91**:1881 (Dec. 15) 1928.

24. Goodpasture, E. W.: J. Exper. Med. **35**:407, 1921.

25. Karsner, H. T.; Saphir, O., and Todd, T. W.: Am. J. Path. **1**:351, 1925.

26. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, ed. 2, Berlin, 1882, p. 38.

27. Wright, S.: Applied Physiology, New York and London, Oxford University Press, 1926, p. 128.

rest. Increased coronary flow was asserted by Rosenbach [28] and Thorel [29] to be a factor in, but not the cause of, cardiac hypertrophy; the increased coronary flow with increased nutrition followed the increased activity. In hyperthyroidism with the increased output per minute, there is an increase in coronary flow and an opportunity for augmented nutrition. But this is more or less counterbalanced by the shortened resting period of the heart due to the tachycardia, and by the increased metabolism.

Herring [12] estimated an increase of 123 per cent in heart weight in thyroid fed male rats and of 59 per cent in females. He believed that this increase could not be accounted for solely on the basis of increased metabolism, but that there was an added factor in the increased epinephrine output which he had shown occurs with thyroid feeding.[30] In five of our dogs the adrenal glands of which were weighed, the mean adrenal gland weight-final body weight ratio was 40 per cent greater than the mean adrenal gland weight-body weight ratio in twenty-two normal dogs. In inanition, the adrenal glands appear to decrease in weight in about the same proportion as does the body as a whole, although some investigators found an increase rather than a decrease in the weight of these glands during starvation (review of literature by Jackson [3]).

While no definite explanation of the at least relative hypertrophy of the heart in hyperthyroidism is evident, it would appear that the increased coronary flow together with increased work may be important factors.

THE EFFECT OF HYPERTHYROIDISM AND INANITION ON THE LIVER

The liver weight-body weight ratio is not constant because this organ is a storage depot for protein, fat and glycogen. Schöndorf [31] found that the liver weight-body weight ratio of dogs fed a high carbohydrate diet was 0.0640. Profitlich [32] found that on a high protein diet this ratio was 0.0350, and Gross,[33] that it was 0.0417. Gerhartz [34] pointed out that this ratio also varies with the age of the dog: in the first week of life, it was 0.0390; in the second week, 0.0430; in the thirty-fourth week, 0.0364; in adult dogs, 0.0265. Junkersdorf [20] found the normal ratio to be 0.0300.

28. Rosenbach, O.: Arch. f. exper. Path. u. Pharmakol. **9**:1, 1878.
29. Thorel, Charles: Ergebn. d. allg. Path. u. path. Anat. **17**:90, 1915.
30. Herring, P. T.: Quart. J. Exper. Physiol. **11**:47, 1917.
31. Schöndorf: Arch. f. d. ges. Physiol. **99**:191, 1903.
32. Profitlich: Arch. f. d. ges. Physiol. **119**:465, 1907.
33. Gross: Verhandl. d. deutsch. path. Gesellsch. **21**:196, 1926.
34. Gerhartz, H.: Arch. f. d. ges. Physiol. **135**:160, 1910.

In our series of thirty-one normal dogs, the mean liver weight-body weight ratio was 0.0303 (table 3).

Jackson [2] quoted Bidder and Schmidt and Bourgeois to the effect that the liver loses weight in starvation more rapidly than the body as a whole, a conclusion in which Jackson [35] himself concurred. Junkersdorf [36] found that the liver lost weight more rapidly than the body in dogs fasting eleven days, and that this loss was roughly proportional, with individual variations, to the loss of body weight and to the original glycogen content of the liver. E. Voit [37] asserted that the liver may lose 50 per cent of its weight during starvation. Pflüger [38] and Schöndorf [39] each starved dogs for twenty-eight days and found that the liver weight-body weight ratio was 0.0150 and 0.0194, respectively. Witsch [19] concluded that the liver had lost 22 per cent of its weight in three dogs which had been starved until they had lost 49, 50 and 60 per cent, respectively, of their original body weights. She concluded that loss of glycogen accounts for practically the entire reduction in dry substance in the livers of these dogs. There was an actual increase of fat. She did not agree with C. Voit [40] and Awrorow [41] that the liver actually increases in weight at the expense of other organs during starvation. Rous and McMaster [42] came to the tentative conclusion that a comparison of the weight of the liver with that of the soft parts of the body shows that, relatively, the liver is three fourths as large in a rat suffering from extreme inanition as in a well nourised rat. In their series, the mean loss of body weight was 33.9 per cent, while the mean loss of liver weight (liver weight calculated for original body weight with use of 0.0410 as the normal ratio for rats) was 53.2 per cent.

In Krieger's [17] series of 123 cases of inanition in man (table 1), the estimated average loss of liver weight was 9.6 per cent less than the estimated average loss of body weight.

Hoskins [11] and Hewitt [13] asserted, as a result of their experiments on rats, that hypertrophy of the liver occurs during the feeding of thyroid. The former calculated that the increase in absolute liver weight was 26.7 and 30.5 per cent in older and younger females, respectively; and 24.4 and 6.4 per cent in older and younger males.

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35. Jackson, C. M.: Am. J. Anat. **18**:75, 1915.
36. Junkersdorf, P.: Am. J. Anat. **186**:238, 1921.
37. Voit (footnote 15, p. 167).
38. Pflüger, E.: Arch. f. d. ges. Physiol. **119**:117, 1907.
39. Schöndorf, B.: Arch. f. d. ges. Physiol. **67**:438, 1897.
40. Voit, cited by Witsch (footnote 19).
41. Awrorow, cited by Morgulis (footnote 1).
42. Rous, P., and McMaster, P. D.: J. Exper. Med. **39**:425, 1924.

In our experiments, the liver was removed immediately after death before the blood had coagulated. It drained out rapidly while the diaphragm and gallbladder were being dissected off. Hence the blood content of these livers was reduced to a minimal and comparable amount.

The coefficient of correlation between liver weight and body weight (column 3, table 2), is not as great as those of correlation between heart and kidney weights and body weight. This is, as already pointed out, probably due to the variations in the quantity of stored material in the liver due to variations in the diet of the animal. In inanition, the correlation between liver weight and final body weight was greater than the normal, while in thyrotoxicosis it was so low as to suggest that there is practically no correlation between these weights. The

TABLE 5.—*The Difference Between the Actual Weight of the Liver and the Weight Calculated for the Final Body Weight*

Dog	Days of Thyroid Feeding	Original Body Weight, Kg.	Final Body Weight, Kg.	Per Cent Loss of Body Weight	Actual Liver Weight, Gm.	Calculated Liver Weight for Final Body Weight,* Gm.	Per Cent Difference Between Actual and Calculated Liver Weight
1	48	11.9	10.2	14.2	397	312	+21.4
2	49	14.5	11.35	21.7	382	344	+ 9.9
3	57	11.6	8.8	24.2	390	267	+31.5
4	93	14.6	10.25	29.8	398	313	+21.5
5	82	9.7	6.75	30.4	301	190	+36.6
6	32	11.9	8.04	33.5	435	343	+44.0
7	70	9.2	5.9	35.8	260	179	+31.0
8	57	10.5	6.7	36.1	360	204	+43.5
9	91	15.85	9.65	39.2	317	294	+ 7.3
10	100	13.9	7.39	46.5	415	224	+46.2
Mean—thyrotoxicosis.....				31.0	362	255	+26.0
Mean—inanition.....				21.0	229	245	—12.0

* The figures in this column were obtained by multiplying the final body weight in grams by 0.303, the normal ratio between body weight and liver weight.

reason for this lack of correlation is evident in table 3, where it is seen that the mean normal liver weight-body weight ratio is 0.0303; while the mean liver weight-final body weight ratio in inanition is 0.0298 and in thyrotoxicosis is 0.0430.

In our series of thyrotoxic dogs, the actual liver weight was in every instance greater than the liver weight calculated for the final body weight, as is shown in table 5. The mean difference was 26 per cent greater, although the mean loss of body weight was 31 per cent; while the mean difference in inanition was 12 per cent less in a group of dogs in which mean loss of body weight was 21 per cent.

In table 6 is shown the per cent gain or loss in liver weight in inanition and thyrotoxicosis. In this table, the liver weight was calculated by multiplying the original body weight by the normal ratio of 0.0303. In inanition, the actual liver weight was less than the calculated weight in all except one animal, which had lost 14 per cent of its body weight; in the thyrotoxic series, the actual liver weight was greater

than the calculated weight in five of the ten animals studied. In thyrotoxicosis, there was a mean loss in liver weight of only 0.475 per cent, although the mean loss of body weight in these animals was 31 per cent. In inanition, the mean loss of liver weight was 30 per cent, while the mean loss of body weight was 21 per cent. From these figures it is seen that in thyrotoxicosis the liver does not lose weight in the same proportion as the body as a whole; while in starvation, the liver, so far as these figures go, loses weight in greater proportion. This is in harmony with Jackson's [35] view, which we have quoted. This is

TABLE 6.—*The Per Cent Gain or Loss of Liver Weight in Inanition and Thyrotoxicosis*

Inanition				Thyrotoxicosis			
Per Cent Loss of Body Weight	Calculated Liver Weight for Original Body Weight,* Gm.	Actual Liver Weight, Gm.	Percentage Gain or Loss of Liver Weight	Per Cent Loss of Body Weight	Calculated Liver Weight for Original Body Weight,* Gm.	Actual Liver Weight, Gm.	Percentage Gain or Loss of Liver Weight
14.0	215.0	237.5	+10.5	14.3	362.0	397.0	+ 9.7
14.6	227.5	176.0	—22.6				
21.5	264.0	153.5	—42.0	21.7	438.0	382.0	—12.8
21.0	188.0	187.5	— 0.03				
24.5	233.0	159.0	—31.5	24.2	350.0	390.0	+11.4
25.0	158.0	131.5	—16.8				
28.5	182.0	160.5	—11.8	29.8	440.0	398.0	— 9.5
29.0	222.0	191.5	—13.8				
29.3	280.0	150.0	—46.5				
35.0	204.0	131.0	—35.7	30.4	295.0	301.0	+ 2.05
				33.5	358.0	435.0	+21.5
				35.8	277.0	260.0	— 6.2
				36.1	315.0	360.0	+14.3
				39.2	480.0	317.0	—34.0
43.5	470.0	145.0	—69.0	46.5	420.0	415.0	— 1.2
49.0	612.0	245.0	—60.0				
Mean	270.8	175.0	—30.0		376.0	372.0	— 0.475

* The figures in these columns were obained by multiplying the original body weight in grams by 0.0308, the normal ratio between body weight and liver weight.

shown even more clearly in table 7, in which the mean, minimum and maximum liver weight-original and final body weight ratios are compared with the corresponding ratios for normal animals. Here it is seen that the mean liver weight-original body weight ratio in thyrotoxic dogs was 0.03 per cent greater, while in inanition it was 22 per cent less than the normal liver weight-body weight ratio. In thyrotoxicosis, the mean liver weight-final body weight ratio was 42 per cent greater, and in inanition 1.7 per cent less, than the normal. The same differences are evident in the minimum and maximum ratios, except in the case of the maximum liver weight-original body weight ratio.

Witsch [19] concluded that the loss of liver weight in starvation could be accounted for by the loss of glycogen. Feeding thyroid also causes complete or almost complete loss of glycogen from the liver, as shown

by Schryver,[43] Cramer and Krause,[44] Parhon [45] and Fukui.[46] Hence, since in thyrotoxicosis there is practically no actual loss of liver weight, something must occur in this organ to counterbalance this loss of glycogen. Just what this is we are not at present prepared to state. Rous and McMaster [42] concluded that the changes which occur in the liver during fasting are essentially conditioned by functional demands made on the liver. With the markedly increased metabolism in hyperthyroidism, it is probable that the functional activity of the liver is greatly increased. This increased activity may take one or both of two directions. In the first place, it is well known that in hyperthyroidism there is a marked increase in the excretion of urea, in the formation

TABLE 7.—*The Per Cent Difference Between Liver Weight-Body Weight Ratios in Normal, Thyrotoxic, and Starved, Dogs*

	Thyrotoxicosis		Inanition	
Ratios Compared	Per Cent Difference*	Percentage of Loss of Body Weight	Per Cent Difference*	Percentage of Loss of Body Weight
Mean L.W./N.B.W.† Mean L.W./O.B.W.	+ 0.03	31.0	—22.0	21.0
Mean L.W./N.B.W. Mean L.W./F.B.W.	+42.0	31.0	— 1.7	21.0
Minimum L.W./N.B.W. Minimum L.W./O.B.W.	+10.4	39.2	—48.0	43.5
Minimum L.W./N.B.W. Minimum L.W./F.B.W.	+78.0	39.2	—13.6	20.0
Maximum L.W./N.B.W. Maximum L.W./O.B.W.	—23.0	33.5	—20.7	21.0
Maximum L.W./N.B.W. Maximum L.W./F.B.W.	+18.8	46.5	+ 1.5	23.8

* The figures indicate the degree to which the second ratio in each pair is greater or less than the first, or normal, ratio.
† L.W. = liver weight; N.B.W. = normal body weight; O.B.W. = original body weight; F.B.W. = final body weight.

of which the liver plays the chief rôle, as shown by Bollman, Mann and Magath.[47] In the second place, the increased metabolism of hyperthyroidism calls for an increase of available and utilizable carbohydrate for energy requirements. The liver is depleted of its glycogen, and the blood sugar is not increased because it is burned at such a rapid rate. Cramer [48] considered glycogen as a specific product of secretion of liver cells. The glycogenic function of the liver is, he thought, an autonomous secretory function by which the liver produces carbohydrate in the form of glycogen independently of any supply of preformed

43. Schryver, S. B.: J. Physiol. **32**:159, 1905.
44. Cramer, W., and Krause: Proc. Roy. Soc., series B **86**:550, 1913.
45. Parhon, M.: J. de physiol. et de path. gén. **15**:75, 1913.
46. Fukui, T.: Arch. f. d. ges. Physiol. **210**:410, 1925.
47. Bollman, J. L.; Mann, F. C., and Magath, T. B.: Am. J. Physiol. **69**:371, 1924.
48. Cramer, W.: Brit. J. Exper. Path. **5**:128, 1924.

carbohydrate in the food and secretes it into the blood in the form of dextrose. Stimulation of the glycogenic function of the liver by the thyroid and suprarenal hormones leads in the normal organism to increased oxidation of carbohydrates, increased formation of carbohydrates from protein, increased heat production and increased nitrogen excretion. If Cramer's idea is correct, there is a marked increase in the functional activity of the liver in the production of utilizable carbohydrate, which is oxidized so rapidly that it does not accumulate in the liver as glycogen nor in the blood as dextrose. Further indication of increased activity on the part of the liver in hyperthyroidism is evidenced by the finding of impairment of liver function in twenty-two of forty-four cases of thyrotoxicosis by Youmans and Warfield.[49] This impairment was in some degree associated with loss of body weight.

This increased functional activity and the increased rate of blood flow are probably important factors in the failure of the liver to lose weight in proportion to the body as a whole in hyperthyroidism. This may, perhaps, be considered a relative, if not an actual, hypertrophy.

THE EFFECT OF THYROTOXICOSIS AND INANITION ON THE KIDNEYS

In his monograph, Jackson[2] quoted Carville and Bochefontaine (1875), Luciani and Bufalini (1882) and Falck (1875) to the effect that in starvation the kidneys are small and atrophic. In his later work, Jackson[35] asserted that in inanition the kidneys lose weight relatively somewhat less than the body as a whole, thus gaining in relative weight; but in absolute weight, the kidneys lost 25.5 per cent in acute inanition anad 26.8 per cent in the chronic form. Witsch[19] observed a relative increase in kidney weight in the three dogs which she had starved until they lost from 49 to 60 per cent of their original body weight.

Hewitt[13] and Hoskins[11] asserted that the feeding of thyroid to rats causes hypertrophy of the kidneys. Hoskins calculated that there was an increase in absolute weight of 46.3 and 33 per cent, respectively, in older and younger females; and 44.4 and 40.4 per cent in corresponding males.

There is a fairly close correlation between body and kidney weight in normal dogs, as may be seen in column 2 of table 2. In starvation, the coefficient of correlation is slightly greater than normal, while in thyrotoxicosis it is considerably less. This indicates that in starvation the kidneys lose weight in about the same proportion as the body as a whole, while in thyrotoxicosis there is a disproportionate loss of weight in either the kidneys or the body.

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49. Youmans, J. B., and Warfield, L. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, Arch. Int. Med. **37**:1 (Jan.) 1926.

Table 3 shows that in thyrotoxicosis the mean kidney weight-original body weight and final body weight ratios are both greater than the normal, while in inanition both ratios are less than normal. This indicates that in thyrotoxicosis the kidneys do not lose weight in the same proportion as the body.

TABLE 8.—*The Per Cent Difference Between the Actual Kidney Weight and the Kidney Weight Calculated for the Final Body Weight*

Dog	Days of Thyroid Feeding	Original Body Weight, Kg.	Final Body Weight, Kg.	Per Cent Loss of Body Weight	Actual Kidney Weight, Gm.	Calculated Kidney Weight for Final Body Weight,* Gm.	Per Cent Difference Between Actual and Calculated Kidney Weight
1	48	11.9	10.2	14.3	71.0	58.0	+18.3
2	49	14.5	11.35	21.7	83.5	65.0	+21.3
3	82	9.7	6.75	30.4	63.0	38.5	+38.7
4	32	11.9	8.04	33.5	72.5	46.0	+35.3
5	70	9.2	5.7	35.8	62.0	35.0	+41.7
6	57	10.5	6.7	36.1	66.5	38.5	+42.0
7	91	15.85	9.65	39.2	74.5	55.0	+25.5
8	100	13.9	7.4	46.5	62.5	42.5	+32.0
Mean—thyrotoxicosis				31.7	69.0	47.5	+32.5
Mean—inanition				25.8	56.7	62.5	−12.0

* The figures in this column were obtained by multiplying the final body weight by the normal kidney weight-body weight ratio of 0.0057.

TABLE 9.—*The Per Cent Gain or Loss in Kidney Weight in Thyrotoxicosis and Starvation*

Inanition				Thyrotoxicosis			
Per Cent Loss of Body Weight	Calculated Kidney Weight for Original Body Weight,* Gm.	Actual Kidney Weight, Gm.	Percentage Gain or Loss of Kidney Weight†	Per Cent Loss of Body Weight	Calculated Kidney Weight for Original Body Weight,* Gm.	Actual Kidney Weight, Gm.	Percentage Loss or Gain in Kidney Weight†
10.0	56.0	39.0	−30.0	14.3	67.5	71.0	+ 5.2
15.2	75.0	61.5	−17.3	21.7	82.5	83.5	+ 1.2
17.3	137.5	124.2	−11.1	30.4	55.0	63.0	+14.6
19.0	92.5	53.0	−42.5	33.5	68.0	72.5	+ 4.5
20.0	114.5	64.1	−44.0	35.8	52.5	62.0	+18.0
20.5	45.5	33.3	−26.7	36.1	60.0	66.5	+ 6.5
20.7	23.5	15.7	−33.4	39.2	90.5	74.5	−17.7
21.8	122.0	69.8	−42.5	46.5	79.5	62.5	−21.5
29.3	52.5	39.0	−25.7				
36.7	85.5	77.0	−10.0				
43.2	88.0	63.3	−28.0				
49.0	114.0	59.3	−47.5				
Mean	83.9	58.2	−29.9		69.4	69.4	+ 1.3

* The figures were obtained by multiplying the original body weight by the normal kidney weight-body weight ratio of 0.0057.

† For the purposes of this table, the per cent gain or loss of kidney weight was estimated by calculating the kidney weight (normal K.W./B.W. ratio = 0.0057) for the original body weight. This calculated kidney weight was compared with the actual kidney weight in each animal in the series.

In table 8 the kidney weight calculated by multiplying the final body weight by the normal ratio 0.0057 is seen to be less than the actual kidney weight in every one of the eight animals studied. The mean per cent difference in the last column of the table shows that the actual kidney weights of the series were 32.5 per cent greater than the cal-

culated weights, although the mean loss of body weight for the series was 31.7 per cent. A similar computation was made for a series of starved dogs data for which were collected from the literature.[50] In the starved animals, the mean actual weight was 12 per cent less than the mean calculated weight. In this series, the mean loss of body weight was 25.8 per cent.

In table 9, the difference between actual kidney weight and kidney weight calculated for the original body weight is shown. The mean actual and calculated weights in thyrotoxicosis were equal; in inanition, the mean actual kidney weight was 29.9 per cent less than the calculated weight. This indicates that the kidney weight was maintained in thyrotoxicosis in spite of the fact that there was a mean loss of body weight

TABLE 10.—*The Per Cent Difference Between Liver Weight-Body Weight Ratios in Normal, Thyrotoxic, and Starved, Dogs*

Ratios Compared	Thyrotoxicosis		Inanition	
	Per Cent Difference*	Percentage of Loss of Body Weight	Per Cent Difference*	Percentage of Loss of Body Weight
Mean K.W./N.B.W. Mean K.W./O.B.W.	+ 5.3	31.7	—29.7	25.8
Mean K.W./N.B.W. Mean K.W./F.B.W.	+49.0	31.7	— 3.5	25.8
Minimum K.W./N.B.W. Minimum K.W./O.B.W.	+ 4.7	46.5	—30.2	49.0
Minimum K.W./N.B.W. Minimum K.W./F.B.W.	+60.4	14.3	— 7.0	20.0
Maximum K.W./N.B.W. Maximum K.W./O.B.W.	—19.8	35.8	—35.0	36.7
Maximum K.W./N.B.W. Maximum K.W./F.B.W.	+29.5	35.8	—11.2	43.2

* The figures indicate the degree to which the second ratio in each pair is greater or less than the first, or normal, ratio.

of 31.7 per cent; while in starvation there was a mean loss of approximately 30 per cent in kidney weight in a series of dogs whose mean loss of body weight was only 25.8 per cent.

In table 10, the mean, minimum and maximum kidney weight-original and final body weight ratios are compared with the corresponding normal ratios. From this table it may be seen that the mean kidney weight-original body weight ratio was 5.3 per cent greater in thyrotoxicosis, and 29.7 per cent less in inanition, than the normal ratio. The mean kidney weight-final body weight ratio in thyrotoxicosis was 49 per cent greater and in starvation 3.5 per cent less, than the normal mean ratio. Much the same differences are shown in the minimum and maximum ratios.

This apparent relative hypertrophy of the kidneys is, perhaps, explainable on the same basis as the apparent relative hypertrophy of

50. Junkersdorf et al. (footnotes 20, 21, 22).

the heart and liver; namely, increased work (excretion of an excess of urea and other products of augmented metabolism) and increased blood flow (increased volume per stroke and output per minute of the heart).

COMMENT

From the data presented it appears that in starvation the heart and kidneys lose weight in about the same or slightly less proportion than the body as a whole, while the liver loses in distinctly greater proportion. This corresponds with Hayashi's conclusion (cited by Jackson [3]) that in inanition the heart and kidneys lose weight more slowly, and the liver more rapidly, than the body. In thyrotoxicosis there appears to be a hypertrophy, relative or actual, in all three organs.

Witsch [19] believed that the incongruity between the relative weights of the liver under physiologic conditions and in hunger inanition is due to the fact that the skeleton takes little part, only about 5 per cent, in the loss of body weight in inanition. Rous and McMaster [42] stated that a comparison of the liver weight in mice with that of the soft body (net body weight less the weight of the ligamentous skeleton) brings out the fact that the organ is, relatively speaking, three fourths as large at extreme inanition as in the well nourished animal. We did not dissect away the soft parts in our animals and weigh them separately. However, E. Voit [37] calculated that in a well nourished dog the skeleton constitutes 15 per cent of the body weight and in starvation 23 per cent. Using these figures, we calculated the original and final soft body weights for each animal in the starved and thyrotoxic series and for the normal dogs, and then calculated the ratios of the organ weights to the soft body weights and compared them with the corresponding normal ratios. The actual ratios were different; but the comparative results differed so slightly from those given that it has not been thought worth while to record them in detail.

In starvation, the animal is deprived of all food; the metabolic rate is lowered, except for the slight increase in the initial days described by Kunde; [51] and the animal becomes inactive. In experimental hyperthyroidism, on the other hand, the dog takes the normal amount or even an excess of food; the metabolic rate is increased, and the animal is hyperactive. One would be warranted, therefore, in presupposing a difference in the part played by individual organs in the general loss of body weight in hyperthyroidism and inanition, respectively. The facts presented bear out this *a priori* supposition.

The apparent relative, if not absolute, hypertrophy of the heart, liver and kidneys in hyperthyroidism is explained, perhaps, by the same causes in the case of each organ; namely, increased function and aug-

51. Kunde, Margaret M.: Am. J. Physiol. **63**:401, 1922-1923.

mented blood flow through the organ. The thyroid gland in these animals was in every case small, and this organ certainly was not called on for increased functional activity under the conditions of these experiments, although the blood flow through it was probably increased just as it was through other organs of the body. Hence it would seem that both increased function and increased nutrition are essential factors in hypertrophy.

In inanition there is decreased activity and decreased function of most of the organs, including the heart. In this condition, therefore, the two chief factors in hypertrophy of an organ, increased function and increased nutrition, are absent. Hence the heart and kidneys, the functions of which are less reduced than those of other organs, lose weight in relatively less proportion than does the liver, and in about the same proportion, or slightly less, than the body as a whole. The liver, on the other hand, in inanition, loses its glycogen and it is not called on for increased production of urea as in hyperthyroidism. Hence the liver loses weight in greater proportion than the body as a whole in starvation.

SUMMARY

In both inanition and experimental hyperthyroidism, the animal as a whole loses weight; but the part played by the individual organ is different in the two conditions.

In starvation, the heart loses weight in about the same or somewhat smaller proportion than the body as a whole. In experimental hyperthyroidism, not only may the heart not lose weight, but in some animals it may appear to increase in size, for the actual weight after prolonged thyroid feeding may be greater than the estimated heart weight at the beginning of the experiment. This apparent hypertrophy is most definite in dogs that have lost from 25 to 35 per cent of their body weight. When the loss of body weight is 40 per cent or more, the effect of experimental hyperthyroidism on the heart appears to be about the same as that of inanition.

The effects of inanition and of experimental hyperthyroidism on the kidneys corresponds rather closely to their respective effects on the heart.

In inanition, the liver loses weight in greater proportion than the body as a whole, and this loss is closely related to the disappearance of glycogen from this organ. In experimental hyperthyroidism, the liver practically maintains its original weight in spite of its loss of glycogen.

The relative, if not absolute, hypertrophy of the heart, liver and kidneys in experimental hyperthyroidism is probably due to the combined effect of increased function and augmented blood flow in each of these organs in this condition.

VARIATIONS IN THE NUMBER OF WHITE BLOOD CELLS IN DOGS FOLLOWING ECK FISTULA *

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An association between the liver and the monocytes seems well established both in man and in animals. The occurrence of monocytosis in catarrhal jaundice was pointed out by Jones and Minot [1] and by Thewlis and Middleton.[2] It has been shown also that there is an increase in the number of monocytes in the guinea-pig following the subcutaneous injection of yellow phosphorus.[3] Lawrence and his associates [4] recently published data to show that following experimental, complete biliary obstruction in dogs and in guinea-pigs there is only a slight increase in the number of circulating monocytes, whereas the number of these cells is more definitely increased following partial biliary obstruction, as was previously found by Holt.[5] We have unpublished data indicating that coal tar in doses sufficient to cause marked hepatic lesions does not produce an increase in the number of circulating monocytes in the rabbit. Additional data on hand tend to show that massive doses of sulpharsphenamine and carbon tetrachloride do not cause increases in the number of monocytes in guinea-pigs even though the livers of the animals may show appreciable lesions. In brief, the relationship between the liver and the circulating monocytes has been studied

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1. Jones, C. M., and Minot, G. R.: Infectious (Catarrhal) Jaundice: An Attempt to Establish a Clinical Entity; Observations on the Excretion and Retention of the Bile Pigments, and on the Blood, Boston M. & S. J. **189**:531, 1923.

2. Thewlis, Ethel, and Middleton, W. S.: The Leukocytic Picture in Catarrhal Jaundice (Cholangitis), Am. J. M. Sc. **169**:59, 1925.

3. Lawrence, J. S., and Huffman, M. M.: An Increase in the Number of Monocytes in the Blood Following Subcutaneous Administration of Yellow Phosphorus in Oil, Arch. Path. **7**:813 (May) 1929.

4. Lawrence, J. S.; Huffman, M. M.; Jones, Edgar; Maddock, S. J., and Nowak, S. J. G.: Variations in the White Blood Cells Associated with Experimental Obstructive Jaundice, to be published in the March issue.

5. Holt, R. B.: Effect on White Blood Cells in Rabbit by Ligation of Common Bile Duct, Proc. Soc. Exper. Biol. & Med. **24**:974, 1927.

clinically in a series of patients with jaundice of various types and experimentally in animals by means of injection of liver intraperitoneally, by treatment with various substances known to be toxic to the liver, and by production of complete and partial biliary obstruction. An increase in the number of circulating monocytes has been found following the injection of phosphorus subcutaneously and of liver intraperitoneally and also in biliary obstruction. The most striking instances of this were found in animals treated with phosphorus.

The next general mode of attack on the problem has been by changes in the vascular supply to the liver. A series of dogs has been studied as regards their white blood cell formulas following the production of Eck fistula with and without splenectomy and also following reverse Eck fistula. Simple Eck fistula has been associated with marked increases in the number of circulating monocytes. Splenectomy combined with Eck fistula has produced less striking increases in the number of monocytes, whereas reverse Eck fistula has been associated with increases of about the same degree as those found following control operations of various sorts.

METHODS

The data reported in this paper are based on observations made on twenty-one dogs, eight of which were used for control operations. One of these (dog 13) was used first as a control and later was subjected to an Eck fistula operation. Dog no. 14 was also used as a control and later for Eck fistula plus splenectomy. Unfortunately, following the second operation this animal developed septicemia and could not be included in the series of dogs on which Eck fistula and splenectomy had been done.

All differential white blood cell counts were made by the supravital method with neutral red. In practically every instance, 200 cells were counted. In a few cases, fixed preparations were made and studied with Wright's stain. A sufficient number of preliminary total and differential counts were made to establish the normal values for each dog prior to operation. In general, all blood counts for a dog were made at approximately the same time of the day. The animals were divided into the following groups:

Group 1.—*Classic Eck Fistula.*—The five animals of the group with classic Eck fistula had been operated on by the cutting string technic invented by Fischler [6] and later modified by Fishback.[7]

Group 2.—*Eck Fistula with Splenectomy.*—The group in which Eck fistula and splenectomy had been performed consisted of four animals. The operation differed from that used for group 1 only in that at the completion of the anastomosis the spleen was removed. The splenectomy was performed by ligation of the splenic artery and later clamping and dividing of the pedicle.

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6. Fischler, F., and Schröder, R.: Eine einfachere Ausführung der Eck'schen Fistel, Arch. f. exper. Path. u. Pharmakol. **61**:428, 1909.

7. Fishback, F. C.: Anastomosis of Portal Vein with Inferior Vena Cava: A Thoroughly Tested and Satisfactory Method of Making an Eck Fistula, Ann. Surg. **86**:436, 1927.

GROUP 3.—*Reverse Eck Fistula.*—The term "reverse Eck fistula," apparently coined by Mann,[8] refers to an operation which differs from the classic Eck fistula operation only in that the inferior vena cava is tied off cephalad to the lumboadrenal vein thus forcing all the blood from the rear portion of the body, as well as the portal blood, to pass through the liver. The operative technic is in other respects essentially the same as that for Eck fistula. There were five animals in this group.

GROUP 4.—*Control Operations.*—Eight dogs were used for control operations. In two of these, one femoral artery and vein were sewed together by a row of continuous sutures, from 5 to 6 cm. long. The needle penetrated the lumina of both vessels with each stitch. One animal (dog no. 20) had a single line of continuous sutures placed in the inferior vena cava so as to make a little tuck in the wall of about the same length as that necessary for the formation of an Eck fistula. Another animal (dog no. 8) had the first part of the operation producing Eck fistula performed; that is, the posterior suture line was inserted as well as the cutting thread. At this point, a hole was torn in the portal vein. This was closed, the cutting thread divided and removed and the abdomen closed. Two dogs (dogs no. 13 and 14) were subjected to simple laparotomies in which an abdominal incision equal in length to that used for the Eck fistula was made. The abdomen was kept open for eighty minutes (a period roughly equivalent to the average time for the production of an Eck fistula) and closed with the usual technic. The last two dogs in the group (dogs no. 10 and 11) had partial ligation of both the portal vein and the inferior vena cava. In this partial ligation, suggested originally by Markowitz [9] as a method for total hepatectomy, both vessels were tied off in such a way that about four fifths of the lumina were occluded.

Following operation, daily total and differential white blood cell counts were made for all the dogs, with a few exceptions. After the first five days following operation total and differential counts were made at varying intervals (from one to twenty-three days). The longest time that any dog was studied was 115 days (dog no. 1). For this animal, twenty-seven different white cell counts were made after operation during a period of 106 days. The shortest period of postoperative study was five days (dog no. 18). The smallest number of white blood cell counts and supravital differential counts after operation was five (dogs no. 18 and 2). The greatest number was twenty-seven (dog no. 1).

The animals were not put to death at the end of the period during which the blood was studied, but were kept alive for use in other experiments. One dog survived the Eck fistula operation for 202 days, at the end of which time it was in a moribund condition and was killed. Complete postmortem studies of the animals used in this study have not been made.

Determinations of the oxygen capacity of the blood by means of the Van Slyke method were made before and after operation in five of the dogs (dogs no. 20, 13, 14, 16 and 15), and after operation in six additional dogs (dogs no. 9, 8, 6, 7, 17 and 19).

A variety of types of dogs, both male and female, were used. Two pregnant dogs were included in the series. Dog no. 9 gave birth to a litter of puppies fifteen days after an operation in which the femoral artery and vein were sewed together. Dog no. 21 was found to have one full term viable puppy in utero at operation. This was removed by cesarean section before the reverse Eck fistula was made.

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8. Mann, F. C.: Studies in the Physiology of the Liver: I. Technic and General Effects of Removal, Am. J. M. Sc. **161**:37, 1921.

9. Markowitz, J., and Soskin, S.: A Simplified Technique for Hepatectomy. Proc. Soc. Exper. Biol. & Med. **25**:7, 1927-1928.

RESULTS

All figures, unless otherwise specified, are for the average counts made on each of the first five days following operation. The maximal number of monocytes was found in this interval in all but three instances (dogs no. 4, 5 and 15). The maximal number of monocytes in dog 4 was found on the sixth day, but no blood count had been made on the fifth day. In dog no. 5 there was only a slight rise in monocytes before the fifth day, but it became more definite after the sixth day. In dog no. 15, the peak of the monocyte rise came on the seventh day, but there was also a definite rise during the five day period. The data for each of the groups have been collected separately.

GROUP 1.—*Classic Eck Fistula.*—1. The principal average operations as regards the white blood cells of this group of five dogs were: The total number of white cells per cubic millimeter increased, on the average, from 12,263 to 26,547 (116.4 per cent). The smallest increase was in dog 4, in which the preoperative total average count per cubic millimeter was 9,450 and the postoperative average total count was 11,817 (25.0 per cent). The counts for the other four dogs of the group were consistent.

2. The neutrophils increased in number tremendously, the average preoperative number per cubic millimeter being 7,833 and the average postoperative number per cubic millimeter, 20,372 (160.1 per cent). Dog 4 was the only one the count for which was not consistent; it showed a postoperative increase of only 2,254 neutrophils per cubic millimeter (from 6,376 to 8,630).

3. The eosinophils decreased in number. The greatest average percentage decrease was in dog no. 4 (89.3 per cent). The maximal average decrease in actual number was in dog no. 13, and was 2,789 per cubic millimeter (73.9 per cent). The average normal number per cubic millimeter for the group was 1,312, and the average postoperative number was 468, a drop of 64.3 per cent.

4. The average number of lymphocytes per cubic millimeter diminished slightly following operation (24.6 per cent), the preoperative value being 1,384 and the postoperative value being 1,043. This reaction was not constant. Two of the dogs showed practically no change (nos. 1 and 15). Two others (dogs no. 3 and 4) showed only a slight drop, and the remaining animal (dog no. 13) had an appreciable postoperative drop.

5. There was a marked increase in the number of monocytes in the blood following operation. The average normal value per cubic millimeter for the group was 1,615, whereas the average value following operation was 4,475. This is an increase of 177.1 per cent. All the

animals of the group showed an increase in the number of the monocytes postoperatively, but the greatest increases were in dogs no. 1, 3 and 15, the last animal showing an increase of 284.6 per cent (from 1,695 to 6,519 per cubic millimeter). Dog no. 4 was not studied on the fifth day, and had shown only a slight increase prior to this. On the sixth and seventh days, however, it showed an increase commensurate with the increases in the other dogs in this group. Dog no. 13 had low values for monocytes throughout a period of seven days after operation, the highest value being 2,961 per cubic millimeter on the second day after operation. This dog had previously been used for a control operation in which a simple laparotomy with exposure of the inferior vena cava and portal vein was done. Blood counts were made on dog no. 1 for 106 days after operation. The monocytic curve gradually returned toward the normal and by the thirty-third day had reached approximately the basic level, at which it remained. The maximal level was maintained fairly constantly for fourteen days. Dog no. 3 was killed on the nineteenth day after operation on account of distemper which was first noticed nine days after operation.

A on the chart shows the postoperative average percentage variations of the number of the white blood cells in the dogs in which Eck fistula operation had been performed.

GROUP 2.—*Eck Fistula with Splenectomy.*—The principal observations with regard to the white blood cells in the four dogs of this group were:

1. An increase in the total number of white blood cells following operation. The average normal number per cubic millimeter was 13,293 as against 26,480 following operation (99.2 per cent). All the dogs reacted consistently in this way.

2. The number of neutrophils was considerably increased, the normal average per cubic millimeter being 9,202 and the postoperative average being 22,506 (an increase of 144.5 per cent).

3. A drop of 44.3 per cent occurred in the eosinophils, the average normal value per cubic millimeter being 971 and the average postoperative value being 541. There was a well defined drop in three of the four dogs (dogs no. 6, 7 and 16), but in the fourth animal (dog no. 5) the average postoperative value was slightly higher than the normal. This animal, however, showed a marked drop in the eosinophils immediately after operation, none being present in a count of 200 white cells on the second day after operation.

The number of lymphocytes decreased from 1,339 to 644 per cubic millimeter (51.9 per cent). Dog no. 5 showed the smallest drop (10.4 per cent). Each of the other dogs showed an appreciable postoperative drop.

The number of monocytes increased from 1,639 to 2,595 per cubic millimeter (58.3 per cent). The greatest average percentage increase was shown by dog no. 7 (101.3 per cent); in this dog, the average normal value per cubic millimeter was 1,904, and the average postoperative value was 3,832. The highest single postoperative value for monocytes was 6,962 per cubic millimeter in dog no. 6 on the third day after operation. One of the dogs in this group (no. 16) showed an actual average diminution in the number of monocytes of 29.7 per cent.

B on the chart shows the postoperative average percentage variations in the number of the white cells of the dogs subjected to Eck fistula and splenectomy.

GROUP 3.—*Reverse Eck Fistula.*—The essential white blood cell observations in the five dogs of this group were:

1. There was an increase in the average total number of white cells to 89.6 per cent. The average preoperative number per cubic millimeter was 14,067, and the average postoperative number was 26,679. Each of the dogs showed an increase.

2. The number of neutrophils was increased from 9,670 per cubic millimeter before operation to 22,481 per cubic millimeter after operation. This increase was manifest in every dog.

3. A consistent postoperative diminution in the number of the eosinophils occurred, the average drop being 57.1 per cent.

4. The average value for the lymphocytes following operation was almost the same as that prior to operation, a drop of 9.6 per cent being noted. The response here was not consistent, two of the dogs (dogs no. 2 and 21) showing a definite increase and the others a diminution.

The number of monocytes per cubic millimeter increased from 1,496 before operation to 2,306 after operation (54.1 per cent). Dog no. 17 showed the greatest average percentage increase (90.3 per cent), the average preoperative number per cubic millimeter being 1,293 and the average postoperative number being 2,460. The response of the monocytes was remarkably constant in all of these animals. Only one very high value (5,408 per cubic millimeter) was noted. This occurred in dog no. 18 on the fourth postoperative day, but was not maintained. The next highest value was 3,720 per cubic millimeter in dog no. 17 on the third day after operation.

C on the chart shows the postoperative average percentage variations in the number of the white cells of the dogs with reverse Eck fistula.

GROUP 4.—*Control Operations.*—Two of the control dogs (dogs no. 13 and 14) had had simple laparotomies performed on them. Each showed a mild postoperative leukocytosis. The average increase in the

total number of white cells was 41.8 per cent. The average increase in the number of neutrophils was 76.5 per cent. The drop in eosinophils was of the same degree as that in the dogs of the other three groups (50.8 per cent). There was practically no change in the number of lymphocytes before and after operation. The monocytes had an average value per cubic millimeter of 1,403 before operation and of 2,344 after operation. This represented an increase of 67.1 per cent. *D* on the chart shows the average percentage variations in the number of the white blood cells of dogs after simple laparotomy.

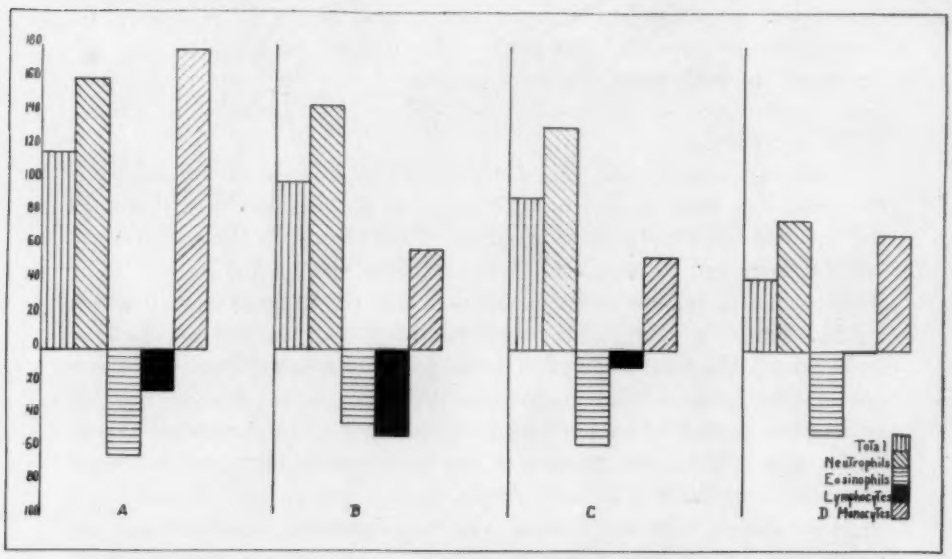
Two dogs (dogs no. 9 and 12) had a line of continuous sutures sewed between the femoral artery and vein. They showed no changes in the total or neutrophilic counts beyond normal limits. The number of eosinophils dropped 29.1 per cent. The number of lymphocytes was depressed in both dogs, the average drop being 48.9 per cent. The number of monocytes increased from 2,250 to 2,641 per cubic millimeter (17.3 per cent).

One dog (dog no. 20) had a midline incision made of the length of the usual Eck fistula. A row of continuous sutures was then placed in the inferior vena cava so as to make a little tuck in the vessel wall, but not sufficient to diminish appreciably the size of the lumen. The location of this trauma to the vessel wall was the same as that in which an Eck fistula is made. This dog showed a well marked neutrophilic leukocytosis, the total number of white blood cells being increased 102.8 per cent and that of the neutrophils 278.3 per cent. The number of eosinophils dropped 51.4 per cent and that of the lymphocytes 50.1 per cent. The number of monocytes per cubic millimeter was increased from 2,078 to 2,558 (23.1 per cent).

Two dogs (dogs no. 10 and 11) had ligatures placed around the portal vein and the inferior vena cava so as to occlude approximately four fifths of the lumina. These showed an average increase in the total white cell count of 61.1 per cent and an average increase in the number of neutrophils of 107.6 per cent. The number of the eosinophils dropped 79.1 per cent and that of the lymphocytes 27.0 per cent. Both these animals reacted alike as regards the aforesaid elements, but they differed in their monocytic responses. In dog no. 10 there was an average postoperative drop of 12.5 per cent and in dog no. 11 an average increase of 94 per cent. The highest value for monocytes in dog no. 11 was 4,862 per cubic millimeter on the second day after operation. The average value for the five days after operation was 3,649 per cubic millimeter. Both these animals had total hepatectomies later.

The remaining dog of the control group (dog no. 8) received marked intravascular trauma to both the vena cava and the portal vein. This animal showed a well marked neutrophilic leukocytosis with a tre-

mendous drop in eosinophils (892.5 per cent), a moderate drop in lymphocytes (57.7 per cent) and a rise in monocytes commensurate with that seen in dogs with Eck fistula (182.9 per cent). On account of this response, the animal was killed on the twentieth day after operation. The most interesting observation at autopsy was the gross evidence of injury to the intima of both the inferior vena cava and the portal vein. No actual blood clot was seen, but histologic section of the vessel in this area showed evidence of an old blood clot. The lymph node normally found lateral and slightly dorsal to the portal vein was somewhat enlarged and hard. There was no positive evi-



The average percentage variations in the number of white cells of dogs following different operations: *A*, following the production of Eck fistula; *B*, following removal of the spleen and the production of an Eck fistula; *C*, following production of reverse Eck fistula, and *D*, following simple laparotomy.

dence of obstruction in either vessel at this time, but the gland was so situated that it could have produced obstruction had it been swollen at any time previously.

To sum up, there was only one dog of this group of eight control animals (dog no. 8) that showed an increase in monocytes of the same order of magnitude as that found in dogs with Eck fistula. This group as a whole showed less leukocytosis than the animals with either the classic or the reverse Eck fistula.

Oxygen Capacity.—The average oxygen capacity for six dogs prior to operation was 22.06 volumes per cent. The average oxygen capacity for two dogs (dogs no. 13 and 15) was 22.28 volumes per cent before operation and for the same animals on the second day after operation it was 23.40 volumes per cent. An average based on one determination for dog no. 13 on the sixth postoperative day and one for dog no. 15 on the fourth postoperative day was 23.48 volumes per cent.

The preoperative oxygen capacity of dogs no. 14 and 16 averaged 23.73 volumes per cent. After these dogs had been subjected to Eck fistula and splenectomy, they showed an average oxygen capacity (one sample on the third and one on the sixth postoperative day) of 22.47 volumes per cent.

COMMENT

The most outstanding result in this series of investigations was the marked increase in the number of the monocytes per cubic millimeter of the circulating blood following Eck fistula. The response was constant in four of five animals. The fifth dog had had a previous laparotomy, which may have influenced the reaction to some extent.

Various possibilities arise when one considers the cause of this monocytic response. One of the simplest explanations is that the spleen normally adds a number of monocytes to the portal circulation, and that these are then filtered off by the liver. The recent work of Menkin [10] showed that the spleen may add an appreciable number of "mononuclears" to the general circulation under the influence of short faradic stimulation. Further, Witts and Webb [11] reported that monocytes and lymphocytes are "much more numerous" in the splenic pulp than in the circulating blood. Hence, it seems reasonable to assume that the spleen may be partly responsible for this increase in the number of monocytes. Further, in support of the assumption are the results which we have obtained in dogs following splenectomy combined with Eck fistula. The average percentage increase in the number of circulating monocytes in the dogs of this latter group was approximately one-third that found in the dogs with Eck fistula alone. However, the response following Eck fistula and splenectomy was too irregular to allow any positive assertions to be made in regard to such a small series of animals. In conformity with the second part of the explanation, namely, the assumption that the liver normally filters off a number of monocytes from the portal blood, are the results obtained

10. Menkin, Valy: The Effect of Splenic Contraction Induced by Faradic Stimulation on the Leucocyte Level of the Splenic Vein, Am. J. Physiol. **88**:737, 1929.

11. Witts, L. J., and Webb, R. A.: The Monocytes of the Rabbit in B. Monocytogenes Infection: A Study of Their Staining Reactions and Histogenesis, J. Path. & Bact. **30**:687, 1927.

after the production of a reverse Eck fistula. The observations in this group of animals as regards the number of circulating monocytes were remarkably constant, and, in no instance, was there a rise comparable to that found in dogs with Eck fistula. It is, of course, well appreciated that the experimental data presented herewith do not justify the presentation of the foregoing explanation in more than a purely speculative way.

Another possibility is that the spleen adds normally to the portal circulation some substance capable of causing an overproduction of monocytes, and that the action of this substance is ordinarily counteracted by passage of the substance through the liver. A similar substance might enter from any other portion of the portal system. In this connection, the question of the food and, hence, of the products of digestion present in the portal blood may be of considerable importance. It may be that only certain articles of food are associated with a marked monocytic response following Eck fistula in dogs. We have not investigated this side of the problem, since all the dogs used by us were fed with a milk and meat diet following operation. Again, changes in the structure and function of the liver after Eck fistula may cause changes elsewhere in the organism, and monocytosis might result from these changes. Removal of the spleen at the time of operation might in some way counteract the tendency to production of monocytes.

One obvious possibility in the case of the dogs with Eck fistula was that injury to the intimal wall caused the monocytic response. The five dogs with reverse Eck fistula, however, had exactly the same amount of intimal damage, but in these dogs the blood was shunted to a large extent through the liver, and it would be impossible to say that this did not counteract any tendency to monocytic response which might have occurred. That this was not the case, however, is indicated in dog no. 20, which had a laparotomy with intravascular trauma to the vena cava. There was only a slight monocytic rise in this dog, the increase being less than in two dogs with simple laparotomies. Further in support of the idea that extraportal intimal damage was not the cause of the appearance of the monocytes in increased numbers in the peripheral circulation were the results in dogs no. 9 and 12, in both of which the femoral vein and artery of one leg were traumatized without any marked rise in the number of monocytes in the blood. The marked increase in the number of the circulating monocytes in dog no. 8 seems to be explained, possibly, by the enlarged gland between the portal vein and the inferior vena cava. This may have produced some degree of obstruction to the flow of blood through the portal vein. The failure to show any increase in the number of the monocytes in one of the dogs (dog no. 10) following partial ligation of the inferior vena cava and the portal vein is additional evidence against intimal

damage being responsible for the rise in the number of the monocytes. The moderate monocytosis in the other dog with partial ligation of both veins is to be expected in such operations, as it is possible that, in this animal, obstruction to the portal blood flow may have been greater than to the flow in the vena cava, in which case we should have had a virtual Eck fistula. The evidence seems to show that intimal damage was not responsible for this reaction on the part of the monocytes.

In order to show that operation alone was not the cause of the increase in the number of monocytes, two dogs (dogs no. 13 and 14) were studied following simple laparotomy. There was some increase in the monocyte count, but this increase was of about the same degree as that found in the dogs with reverse Eck fistula, and those in which Eck fistula and splenectomy had been performed. It was not comparable with that seen in the dogs with Eck fistula.

The degree of anemia was investigated by means of Van Slyke determinations of the oxygen capacity of the blood of some of the dogs. The blood for the determinations of oxygen capacity was obtained from one to eight days after operation. During this period there was only slight evidence of a drop in hemoglobin. Of course, the results obtained on the first one or two postoperative days may have been influenced by vomiting and dehydration, but results obtained at later intervals were probably not influenced by these factors. Dog no. 15, which showed the highest monocytic response of any of the dogs, had an oxygen capacity of 22.53 volumes per cent before operation and one of 21.93 volumes per cent on the fourth day after operation. Therefore, the response cannot be explained by anemia. Further, if the increase in the number of the monocytes had been due to anemia, the marked response of this type should have occurred in the dogs and guinea-pigs with complete biliary obstruction reported by Lawrence and his associates.[4]

Explanation of the monocytosis as secondary to the neutrophilic leukocytosis is not possible, since the monocytic response is out of proportion to the neutrophilic. Moreover, the dogs with Eck fistula plus splenectomy and those with reverse Eck fistula had approximately the same neutrophilic leukocytosis as the dogs with Eck fistula.

The postoperative diminution in the number of the eosinophils is worthy of comment. This was constant for each group of animals. The only exception was dog no. 8, in which there was a great drop (892.5 per cent). The average percentage diminution varied between 29.1 and 79.1. This result has been noted previously by Krumbhaar [12] and more recently by Lawrence and his associates.[4] It is not a

12. Krumbhaar, E. B.: Observations on the Nature of Postoperative Leucocytosis in the Dog, Ann. Surg. **66**:133, 1917.

specific response, but seems to be due to the operation. The extent and severity of the operation may have some effect on this response, as the least drop occurred in the two dogs with traumatized femoral artery and vein.

The response of the lymphocytes was in the same general direction as that of the eosinophils. There was not as much constancy in the lymphocytic reaction as there was in the eosinophilic, however. It is worthy of note that there was a greater average percentage diminution of the number of lymphocytes in the dogs with Eck fistula and Eck fistula plus splenectomy than in those with reverse Eck fistula and simple laparotomy. Since the reaction was inconstant and since there was a commensurate decrease in the number of lymphocytes in some of the control dogs (i. e., those with partial ligation of the inferior vena cava and portal vein and those with traumatized femoral artery and vein and the animal with a traumatized inferior vena cava), one must be careful in drawing any conclusions from their responses. On the other hand, the decrease in the number of lymphocytes in the dogs with Eck fistula and in those animals in which Eck fistula and splenectomy had been performed is well in accord with previous observation in patients with catarrhal jaundice.[13]

SUMMARY AND CONCLUSIONS

Monocytosis of marked degree occurs in dogs within the first week following Eck fistula. Splenectomy done at the same time as the Eck fistula tends to prevent this monocytosis. Dogs with reverse Eck fistula do not show this monocytic response. Intimal damage, anemia and operation are not the responsible factors.

A diminution of the number of eosinophils in the blood of dogs follows operations of various types on the vascular system. The average number of the lymphocytes is constantly diminshed in such dogs.

Possible theoretical explanations of the monocytic response after Eck fistula are offered.

13. Jones and Minot (footnote 1). Thewlis and Middleton (footnote 2).

GIANT CYST OF THE ANTERIOR ABDOMINAL WALL

URACHUS CYST OR ENTEROCYSTOMA?*

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The case to be described forms an addition to the not great number of cases of cysts of the anterior abdominal wall which have already been discussed and classified.

REPORT OF CASE

The cyst was found in a man, aged 70, who had been ill for about two years, with increasing swelling of the abdomen. He had felt only a little discomfort from it. He had grown slightly thinner. On May 1, 1928, he fell down in the street, and as he could not get up again, he was taken to the hospital.

On admission, the patient presented cardiac arrhythmia, with dull sounds, but no murmur. The respiratory organs were normal. The abdomen was greatly distended by fluid. The urine was acid and flaky. The result of the Heller test was negative.

A laparocentesis was performed, May 2. Only a few cubic centimeters of thick, brown fluid was obtained. On account of its density, the fluid did not run out.

A laparotomy was performed, May 4 (Dr. E. Edholm). After a "gridiron" incision of McBurney, one entered a cyst, from which 20 liters (20,000 cc.) of partly creamlike, partly thinly flowing, brownish-yellow fluid was tapped. This procedure was followed by extirpation of part of the cystic wall including a string-like formation.

Histopathologic Examination (Henschen).—The specimen consisted for the most part, of an irregular, dense, fibrous, hyaline, vascular and partly necrotic mass of tissue, rich in crystals of cholesterol. Here and there on the surface and in the interior could be seen simple cylindric epithelium, with goblet cells—probably entodermcystoma. The string contained abundant elastic tissue and muscular fibers, cut lengthwise; it may have been an obliterated vessel.

Course.—After the operation, the patient recovered temporarily, but tension gradually recurred in the cyst, which kept increasing, so that by June 5 there was a question of repeating the drainage. The general condition of the patient, however, did not allow an operation to be performed. During the final days, there was rapid deterioration. The patient died, June 6, 1928.

Clinical Diagnosis.—Cysta abdominalis (enterocystoma? pancreatic cyst?); arteriosclerosis; bronchopneumonia (?).

Postmortem Examination.—Autopsy was performed, June 8, by C. F. Ulfsparre. The body was that of a normally built man, the subcutaneous fat maximally reduced and the muscles somewhat reduced and weak. The skin was pale and cachectic. The thorax was flattened from the front backward to a dish shape. The abdomen was greatly enlarged, especially in its lower parts. When the chest

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* From the Pathological Department of Karolinska Institutet, Professor Folke Henschen, director.

was opened, the cavity was found to be abnormally small. The heart was dilated and weak. The myocardium was brown. Slight endocarditis was present in the mitral ostium, and moderate atherosclerosis in the valves, coronary arteries and aorta. Acute, somewhat hemorrhagic pneumonia was found in the lower right lobe. The diaphragm was greatly pushed upward, standing on a level with the third intracostal space.

When the abdomen was opened, it was difficult to find any free space in the cavity. The whole of the lower part of the abdomen was occupied by a large cyst, which was attached to the posterior sheath of the rectus muscle. In the upper part of the abdomen, the transversum was at once apparent, and was fixed to the cyst by firm adhesions. There were firm adhesions everywhere. The ileum and jejunum were much displaced, upward and backward, to the left. The colon ascendens with the cecum and the appendix lay immediately above the umbilical plane, pressed against the lateral abdominal wall. The intestines were pale and collapsed. The cyst was now isolated as far as possible. In doing this, parts of the posterior sheath of the rectus muscle were taken, too. The adhesions to the adjacent organs were cut through with sharp dissection. The wall of the cyst burst, and an attempt to close the holes by means of Péan's operation was a failure. The anterior wall was therefore cut through, and the cyst was emptied; about 6 liters (6,000 cc.) at first clear yellow, later increasingly muddy, puslike, thinly flowing fluid was obtained. The cyst was taken out together with the pelvic organs and examined more closely. It consisted of a single cavity, firmly attached to the bladder. The wall was about 1 cm. thick, rather dense, especially toward the bladder. The muscular coat of the bladder seemed partly to pass over directly into that of the cyst. On its interior surface, the wall was covered with flaky, greasy matter. In the upper part of the cavity, in addition to the whitish-yellow greasy coat, the wall showed knobby protuberances. The bladder, cut open, was shown to be somewhat inflamed. Somewhat to the right of the median line, in the upper part of the bladder, a little funnel-like diverticulum was found. There was hydrocele of the left testis; the right testis showed fibrous conversion. In the mucous membrane of the stomach were a number of polyps of the usual appearance. There was nothing remarkable about the pancreas. In the gallbladder were a number of gallstones; the gallbladder was shrunken, its wall thickened.

Pathologic Anatomic Diagnosis (Henschen).—Degeneratio fusca and dilatatio cordis; endocarditis chronica verrucosa mitralis; cardioarteriosclerosis; pneumonia haemorrhagica lobi inferioris dextris; *cysta urachi?* (6,000 cc).; hydrocele testis sinistris and fibrosis testis dextris; polyposis ventriculi; aclculi vesicae felleae; cholecystitis chronica retrahens.

Specimens Preserved.—Cyst; urinary bladder; rectum.

Macroscopic Examination.—The specimen obtained at operation, by excision from the wall of the cyst, after being preserved several months in alcohol, consisted of a hard mass, in which one could distinguish only a number of irregularities on the internal wall, together with a peculiar cordlike growth about 0.5 cm. thick in cross-section, which, everything taken into consideration, seemed to have been fastened at one end to the inner surface of the wall.

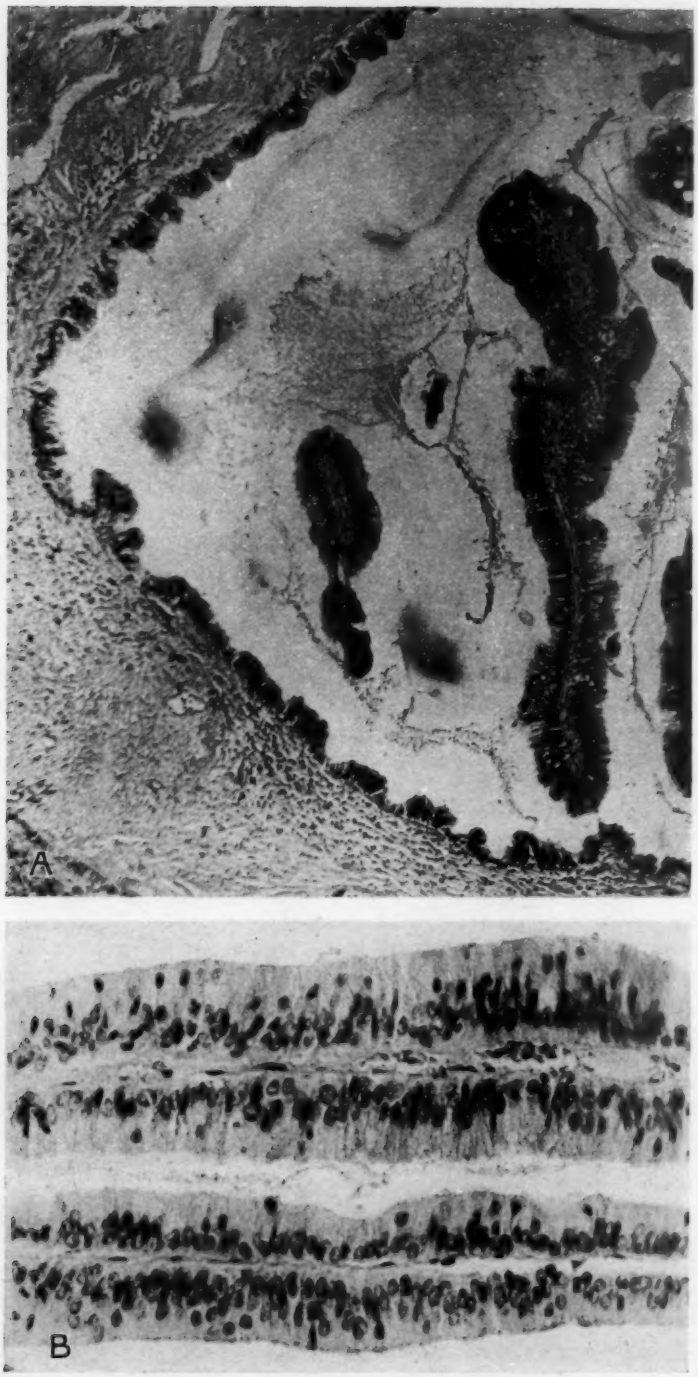
The specimens obtained at the postmortem examination, preserved in a solution of formaldehyde, were the cyst and the urinary bladder, together with the ureters, and the rectum. On closer study, the cyst was seen to be pear-shaped, its greatest diameter being about 30 cm. The rapidly narrowing point, directed caudally, was squeezed down in the median line with a funnel-like depression, between the bladder and the rectum into fossa douglasi. It ended blindly here on a level with

the upper horizontal edge of the trigonum lieutaudi, corresponding in the rectum to a distance of 5 cm. from the annulus haemorrhoidalis. The cyst was only loosely attached to the rectum, but was firmly fixed to the posterior wall of the bladder. The connection with the latter was still further strengthened by the powerful bundles of muscle which somewhat to the right of the median line continued from the wall of the bladder, in front of the funnel-like diverticulum of the vertex, up over the wall of the cyst. The muscular bundles were accompanied by powerful vessels. Along each side of the wall ran the two ureters. Moreover, on the wall could be seen the remnants of adhesions to the adjacent organs (see the account of the postmortem examination). The wall was from 2 to 5 mm. thick, except the part just above the bladder, where the muscular coat lent it a thickness of about 1 cm. The cavity was enclosed everywhere by a dense membrane, which was coated inside with greasy matter. In the upper part, clustered together on a space of about 1 square decimeter, a multitude of papillomatous growths were found, some of them the size of pigeon's eggs, as well as a number of peculiar shreds, which were hanging loose in the cavity. On the right side, was an extensive induration which, on account of the occurrence of more abundant blood pigment, was assumed to be the scar of the operation. On the inner surface of the induration, a cartilaginous formation was found, which had a point, shooting out into the cyst's cavity. It may possibly have something to do with the "cord" that was removed by excision.

Microscopic Examination of the Specimen Obtained at the Operation.—Two different sections were prepared from the wall itself, as well as one from the "cord." In one section the wall, as a whole, was clothed with mucous membrane. Here the wall was formed of loose, fibrillar connective tissue, rich in nuclei and containing necrotic matter here and there. By the use of Weigert's stain for elastin, abundant elastic tissue was shown, especially in a layer immediately beneath the epithelium. The tissue was interlaced with large blood-filled vessels, and in one place much hemorrhage was seen. Small accumulations of lymphocytes were found everywhere. The mucous membrane (fig. 1 *A*) formed numerous papillae, of which a part were long and narrow, with only a thin septum of connective tissue, while others had a vascular stroma that pushed out the mucous membrane causing different formations.

The epithelium of the mucous membrane was cylindric, with goblet cells appearing abundantly here and there (fig. *B*). It was rather irregular. Alternating with stretches of simple epithelium, areas occurred having nuclei in several layers and indications of stratified epithelium. Both in the papillae and between them were numerous glandular crypts. A number of cells had lost the typical cylindric form; this was especially the case on the vertex of many papillae, where the epithelium looked as though it had been transformed into cuboidal cells. The nuclei, generally speaking, lay near the base, and, in some places, like the rest of the cells, took an oblique position in regard to the axis of the papillae. Vacuolated cells recurred everywhere in the mucous membrane; in a number of the papillae, the connective tissue had undergone mucous degeneration. The mucous fluid between the papillae contained red blood corpuscles and leukocytes.

The other section from the wall consisted partly of a necrotic, hyaline mass of tissue, with abundant crystals of cholesterol. In the center of this mass, a hollow was seen, which was coated with epithelium of the same kind as that in the large cyst. Proliferation, however, had not been so great here, for the epithelium was more regular and the wall, with the exception of a limited space where the papillary structure reminded one of that of the large cyst, was furnished with only solitary, insignificant elevations. On the surface of the wall, the mucous mem-



A. Section from the cyst wall showing various papillomatous formations.
B. The irregular cylindric epithelium of the papillae with goblet cells.

brane remained on a little space only. In the center, it consisted of low, cylindric epithelium, which along the sides made way for cuboidal and flat epithelium, and soon ceased altogether. Whether this cavity, which was visible to the naked eye, should be interpreted as a part of the large cyst or as an independent growth must be left undecided.

The cordlike growth consisted, externally, of a layer of hyaline connective tissue with crystals of cholesterol. Inside this were plain muscular fibers enclosing a small portion of hyaline, vascular connective tissue. In the muscles, a layer of longitudinal fibers could be distinguished, and inside this, a layer of circular ones, which was abundantly interlaced with elastic tissue. On account of the almost complete absence of muscular fibers in the cyst otherwise, and because of the characteristic stratification in the cordlike growth, the latter was probably an obliterated vessel.

At the microscopic examination of the wall of the cyst as it appeared after the postmortem examination, the presence of an epithelial coat could not be seen anywhere, although sections from a large number of parts of the wall were examined. This seemed to indicate that the epithelium had completely disappeared. The papillomatous protuberances in the upper part consisted of necrotic matter, and the rest of the wall was covered with a thick layer of necrotic matter, too. The continuity of the muscular coat of the bladder and cyst, which was commented on previously, was thus confirmed by the microscope through the presence of a thick layer of longitudinal smooth muscle fibers, which were common to both organs. These, however, extended only a few centimeters up the wall of the cyst. In the other parts, no muscular fibers were to be found.

COMMENT

After the microscopic examination of the section taken at the operation, the diagnosis of probable entodermcystoma was made owing to the appearance of the epithelium. At the postmortem examination, on account of the intimate, partly muscular connection between the urinary bladder and the cyst, one arrived finally at the diagnosis: cysta urachi. The question now is, which of these diagnoses is to be considered as having the best foundation?

It is difficult to associate the different facts brought to light, in order to formulate an explanation that can be accepted without reservation. I shall therefore present only the result I arrived at in my attempt to clear up the pathogenesis of the cyst, without making any pretension of having succeeded in solving the problem.

Naturally, the rough anatomic figure—I am thinking now especially of the musular continuity between the bladder and the cyst—seems to speak strongly in favor of the cyst's having originated in the urachus.

The urachus appears as a ventral sinus curving out from the posterior part of the intestine, which afterward passes into the entodermal cloaca. After this has been divided in the second fetal month, by the septum urorectale, into the rectum and urogenital duct, the bladder is developed as a part of the latter. Whether the bladder, with the exception of the trigonum lieutaudi, originates entirely in the cloaca or whether the urachus possibly is included in the cranial part

has not yet been established (Broman[1]). The obliteration of the urachus, which sets in during the same month, is never complete; one normally finds the canal in the lower part, usually separated from the bladder by a fold. Enclosing the canal and extending a bit above it, the muscular coat of the bladder continues, with perponderating longitudinal fibers in the lower third part of the urachus (Wutz[2]). Besides this, epithelial strands or epithelium clothed cavities are often found in the ligament, as remmants of the canal. These through independent growth can assume rather considerable dimensions; they often attain a size of from 5 to 6 liters (5,000 to 6,000 cc.), and in two cases, described by Cullen[3] and by Freer,[4] respectively, they had a volume of about 50 liters (50,000 cc.). There has been great interest in urachus cysts during recent decades, and much has been written about them (Dössekker,[5] Hartmann,[6] Kohlfahl,[7] Soulié,[8] Weiser[9] and many others).

Besides the cystic formation the points which the cyst now under discussion has in common with urachus cysts are the preperitoneal position between the bladder and the navel and the connection with the vertex of the bladder. Why it has left the course of the urachus and pushed itself down far behind the bladder is difficult to understand. Instead of wedging itself into the pelvis, it should have taken still more of the abdominal cavity, for there the resistance must have been considerably less.

As may be expected, most urachus cysts are situated on the median line. The reason for the lateral dislocation, which has been proved in some cases, is to be sought probably in the fact that it is not any remnants of the epithelial canal itself but sinuses of the latter that have caused the cysts. Luschka[10] showed that the urachus canal is "furnished with numerous larger or smaller sinuses, which lend it a

1. Broman, I.: Normale und abnorme Entwicklung des Menschen, Wiesbaden, J. F. Bergmann, 1911.

2. Wutz, J. B.: Ueber Urachus und Urachuscysten, Virchows Arch. f. path. Anat. **92**:387, 1883.

3. Cullen, T. S.: The Diseases of the Umbilicus, Philadelphia, W. B. Saunders Company, 1916; cited by Rankin and Parker (footnote 11).

4. Freer, A.: Abnormalities of the Urachus, Ann. Surg. **5**:107, 1887.

5. Dössekker, W.: Klinischer Beitrag zur Lehre von den Urachuscysten, Beitr. z. klin. Chir. **10**:102, 1893.

6. Hartmann, E.: Ueber Urachuscysten, Inaug.-Diss., Halle, 1911.

7. Kohlfahl, A.: Ein Beitrag zur Kenntnis der Urachusresten, Inaug.-Diss., Giessen, 1919.

8. Soulié, J.: Contribution à l'étude des kystes de l'ouraque, Diss., Boredaux, 1919.

9. Weiser, W. R.: Cysts of the Urachus, Ann. Surg. **44**:529, 1906.

10. Luschka, H.: Ueber der Bau des menschlichen Harnstranges, Virchows Arch. f. path. Anat. **23**:1, 1862.

knotty appearance, sometimes even a configuration which is reminiscent of an acinous gland." The sinuses usually touch only a part of the wall, are more or less pedunculated and can be completely isolated. When making his extensive examinations on seventy-four cadavers, Wutz found similar sinuses in nearly a third of the cases. In this way, in my case, an explanation is found for the displacement of the apex of the bladder to the right. The position of the funnel-like hollow of the cyst exactly in the median line is, however, inexplicable. Possibly, it may depend on the circumstance that the cyst during its wandering down into the pelvis was forced, on account of the small space there, to pursue the median line.

The difficulty of determining the genesis of the cyst now under discussion is met with in the character of the epithelium. The covering of transitional epithelium possessed by the urachus at one time recurs chiefly as transitional or flat epithelium in malformations, whether this concerns fistulas, cysts or solid tumors. During recent times, however, there have been some reports of cases of a neoplasm having an epithelium which bears an unmistakable likeness to the intestinal epithelium, but which in every other way, points to a genesis from the urachus. Such is the case of adenoma urachi, described by Rankin and Parker,[11] and such are the cases of adenocarcinoma of the urachus described by Schwarz,[12] Michin[13] and Khaum.[14] Schwarz placed here, too, a case of tumor described by Koslowski[15] under the name of navel adenoma.

Schwarz, in order to clear up the question of the occurrence of glands in the urachus, examined several urachi in numerous sections, but did not find any such tissue. Among the glands met with in the bladder, some have cylindric epithelium (Rauenbusch[16]). Rauenbusch collected seventy-five reports of cases of carcinoma of the bladder, of which two resembled colloid cancer of the rectum. One case, which under the name of "bladder diverticle" has recently been sent to Professor Henschen from Serafimerlasarettet in Stockholm, presented at a microscopic examination of the somewhat inflamed mucous mem-

11. Rankin, F. W., and Parker, B.: Tumors of the Urachus, Surg. Gynec. Obst. **42**:19, 1926.

12. Schwarz, E.: Das Carcinom des Urachus, Beitr. z. klin. Chir. **78**:278, 1912.

13. Michin, W. A.: Zur Kasuistik der aus Resten des Ductus omphalomesentericus sich entwickelnden malignen Neubildungen, Virchows Arch. f. path. Anat. **209**:47, 1912.

14. Khaum, E.: Ueber primäres Karzinom des Urachus, Wien. klin. Wchnschr. **29**:130, 1916.

15. Koslowski, B. S.: Ein Fall von wahrem Nabeladenom, Deutsche Ztschr. f. Chir. **69**:469, 1903.

16. Rauenbusch, L.: Ueber Gallertkrebs der Harnblase, Virchows Arch. f. path, Anat. **182**:132, 1905.

brane, which otherwise was coated with transitional epithelium, agglomerations of transversely cut glandular ducts of the same type as those in the large intestine. (As the diverticulm, as a whole, was not preserved after the operation, it was not possible to study this case more closely). In exstrophic bladders, Enderlen often saw cylindic epithelium with golbet-cells (Schwalbe [17]). This change in the tissue he ascribed not so much cells of a fetal character, as to adaptation caused by external irritation from the air, contact with clothing, etc. This explanation does not appear to be entirely acceptable. Cylindric epithelium, I suppose, must generally be considered as more fragile than transitional. In chronic inflammation, the cylindric epithelium, as is well known, is not infrequently converted into transitional or flat epithelium. Another explanation is more probable: If, from any cause, cells belonging to an early embryonic stage are left lying about without being used for normal development into transitional epithelium, it does not seem improbable that they may follow instead the law of differentiation into intestinal epithelium (Schwarz).

If solid tumors of the urachus with cylindric epithelium are of relatively rare occurrence, a urachus cyst with cylindric epithelium is unique. The adenomatous proliferation of the mucous membrane indicates, however, that in this case one is not concerned with a urachus cyst in the usual meaning, but that, if it really is a urachus malformation, it should be classified with tumors mentioned shortly heretofore. Its enormous size, which gives it a resemblance of the real urachus cyst, must be ascribed to strong secretional activity on the part of the golbet-cells. A diagnosis in accordance with the structure of the cyst should therefore evidently be as follows: adenocystoma papilliserum urachi.[18]

Enterocystomas, according to Roth,[19] are "congenital sacs filled with fluid, the walls of which have, more or less completely, the structure of the intestinal canal." It was Roth who first presented these tumors systematically. He separated them into two different groups: (1) those which arise owing to secondary modifications in the normally disposed intestine, so that it becomes divided into several cystic formations, and (2) those which depend on a primarily abnormal development of the intestine, and which are found together with a permeable intestinal

17. Schwalbe, E.: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1927.

18. Tumor growth in cysts having originally normal urachus epithelium has been described by Hoffman (Flat-Cell Cancer Through Chronic Irritation of an Originally Patent Urachus, Arch. d. Heilk. **11**:373, 1870); Pendl (Colloid Cancer, Beitr. z. klin. Chir. **91**:681, 1914); Utterström and Bergstrand (Eim Fall von properitonealer Riesenzyste in der vorderen Bauchwand, Upsala Läkareförenings förhandl. Nyföljd. **34**:1, 1928.

19. Roth, M.: Ueber Missbildungen im Bereich des Ductus omphalomesentericus, Virchows Arch. f. path. Anat. **86**:371, 1881.

canal. The latter group is divided into three subdivisions: (*a*) cysts belonging to a rudimentary twin;[20] (*b*) combined enterocystomas appearing in connection with other organic displacements (strangulated biliary ducts and numerous groups of liver-like substances;[21] and (*c*) simple enterocystomas arising from abnormal diverticulums of the intestine, most frequently from the diverticulum meckeli or the ductus omphalomesentericus.

Some authors assume that there must be embryonic isolation of the intestinal epithelium to cause enterocystomas; others have limited this assumption to include only the cysts arising from the ductus omphalomesentericus (Kostlivý[22]).

With the atrophy which the ductus omphalomesentericus undergoes at the end of the second fetal month, different malformations can arise, owing to the total or partial persistence of the canal. If the middle part of the canal is left, enterocystomas can arise. They are generally situated on the convex side of the intestine, corresponding to the position of the ductus omphalomesentricus; they are subserous and seldom pedunculated. Following secondary displacements, they may also be met with intramesenterically. A few enterocystomas, like the cyst in question, are situated preperitoneally. Colmers,[23] who made a comparison of thirty-nine enterocystomas, found only four of this type (von Wyss,[24] Roser,[25] Schaad[26] and one of his own). Besides these, Dubs[27] reported one case. However, neither as regards the size nor as regards the relation to the bladder or urachus can points of comparison with the one under discussion be advanced.

However, the ductus omphalomesentericus and the allantois lie enclosed so near to each other in the umbilical ring that it may well be thought that a remnant of the former at its later development happened to accompany the urachus and thus gives a specious appearance of belonging genetically to the latter. In spite of the fact that Michin considered such a development of the tumor described by him as being

20. Schärer, in Klebs: Handbuch der speciellen pathologischen Anatomie, vol. 1, p. 1013.

21. Sänger and Klopp: Arch. f. Gynäk., 1880, vol. 16.

22. Kostlivý, S.: Ein Beitrag zur Aetiologie und Kasuistik der Mesenterialcysten, Deutsche Ztschr. f. Chir. **91**:351, 1908.

23. Colmers, F.: Die Enterokystome und ihre chirurgische Bedeutung, Arch. f. klin. Chir. **79**:132, 1906.

24. Von Wyss, H.: Zur Kenntnis der heterologen Flimmercysten, Virchows Arch. f. path. Anat. **51**:143, 1870.

25. Roser, W.: Ueber Operation der Urachuscysten, Arch. f. klin. Chir. **20**: 472, 1877.

26. Schaad, T.: Ueber die Exstirpation einer Cyste des Dotterganges, Kor.-Bl. f. Schweiz. Arzte **16**:345, 1886.

27. Dubs, J.: Zur Pathologie des persistierenden Ductus omphalo-entericus, Kor.-bl. f. schweiz. Aerzte **46**:1505, 1916.

self evident, he did not hesitate to describe the case as being cystadenocarcinoma urachi. In agreement with the theory mentioned, one should, while avoiding Michin's misleading terminology, consider the most adequate diagnosis to be that of enterocystoma.

The extension of the cyst down even into the fossa douglasi and its firm fixture there lead me, in the meantime, to touch briefly on another possibility.

May it not possibly be thought that the cyst, as it is so firmly wedged between the organs in the pelvis, may have developed just here? Certainly, in such a case it should properly be reckoned as belonging to enterocystoma, taken in the widest sense, but since with this question one enters on the sphere of urorectal fistula, it seems to me more suitable to treat of it in a special division.

It appears to me not altogether unthinkable that with the coalescence of the folds of the urorectal septum or of the septum, on one side, and of the cloacal membrane, on the other, on account of some obstruction, an epithelial germ happened to be enclosed which afterward developed further. In a similar manner, rectovesical fistulas are formed, with this difference only, that the continuity of the epithelium covering the rectum and the sinus urogenitalis within a larger or a smaller area is never broken through by the mesenchyme.

SUMMARY

In a man, aged 70, a cyst of 20 liters (20,000 cc.) was met with on the anterior abdominal wall, having a plainly marked primarily muscular continuity with the bladder and a mucous membrane coated with cylindric epithelium. Three alternative diagnoses are offered in explanation of its pathogenesis: urachus cyst, enterocystoma or a cyst originating as does rectovesical fistula through an incomplete septum urorectale.

PRIMARY CARCINOMA OF THE LUNGS

IV. INTRACRANIAL METASTASES *

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The incidence of intracranial metastases from primary carcinoma of the lungs cannot be ascertained, for the few available statistics often fail to state whether the brain in every one of the included cases was examined. Thus, Dosquet,[1] in a study inspired by Lubarsch, investigated the necropsy material from the institutes of pathology at Kiel and Berlin, respectively, and found metastases to the central nervous system in 33 of 105 cases of bronchiogenic carcinoma. Seyfarth[2] found the brain involved in 30 of 309 necropsies on patients with bronchiogenic cancer, and Levy-Simpson[3] observed intracranial metastases in 19 of 139 postmortem examinations of patients with the same disease. Neither of these authors stated whether the brain was examined in every one of the necropsies of his series.

Thirty-eight proved cases of primary carcinoma of the lungs have been observed by us, and in 15 of these, metastases to the central nervous system were verified either at operation or at necropsy or by both procedures. In the remaining twenty-three cases, either there was no anatomic evidence of metastases to the brain or the central nervous system was not examined. Twelve of the 15 cases were unusual in that they were diagnosed as "tumor of the brain suspects."

That the ever-increasing interest taken in the recognition of tumors of bronchiogenic origin by clinicians, roentgenologists and pathologists should be equally shared by the surgeon is due to the fact that the metastases from the small, and often symptomless, primary pulmonary

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* From the Surgical Department of the Peter Bent Brigham Hospital.

* The preceding papers of this series have been: Fried, B. M.: I. Primary Carcinoma of the Lungs, Arch. Int. Med. **35**:1 (Jan.) 1925; II. Further Study, with Particular Attention to Incidence, Diagnosis and Metastases to the Central Nervous System, ibid. **40**:340 (Sept.) 1927; III. Histogenesis and Metaplasia of Bronchial Epithelium, Arch. Path. **8**:46 (July) 1929.

1. Dosquet: Ueber die Metastasenbildung bei primären Lungen und bronchial Krebses, Virchows Arch. f. path. Anat. **234**:481, 1921.

2. Seyfarth: Lungen Carcinome in Leipzig, Deutsche med. Wchnschr. **50**: 1497, 1924.

3. Levy-Simpson, S.: Primary Carcinoma of the Lung, Quart. J. Med. **22**: 413, 1929.

tumor may themselves simulate primary malignant disease. This fact is of particular importance to the neurosurgeon, for, as has been observed, the tumors under discussion metastasize frequently to the central nervous system, and what is more, the metastases often occur when there is no subjective evidence of the existence of a visceral tumor. It is in these instances that the metastatic tumor simulates the preoperative life history of the most invasive and rapidly growing glioma, the glioblastoma multiforme, and causes such acute intracranial symptoms as to make an intracranial operation an emergency procedure.

The purpose of this study is to discuss the clinical and pathologic observations in intracranial metastases occurring in patients with primary carcinoma of the lungs.

THE PATHWAY OF INTRACRANIAL METASTASES FROM THE LUNGS

The manner in which carcinoma of the lungs reaches the central nervous system has not previously been the object of investigation owing apparently to the fact that the frequent occurrence of this metastasis has not been noticed until recently. The subject is of interest because the spread of cancer, as commonly accepted, is by way of lymphatics, which are lacking in the central nervous system.

The central nervous system was believed to be provided with a double set of lymphatics: (1) the lymphatic spaces of Virchow-Robin and (2) the lymphatic spaces of His.

In 1859, the French pathologist Robin[4] found that cerebral capillaries of a certain caliber (0.33 mm. in diameter) are normally separated from the cerebral tissue by a membrane that surrounds the vessel in a sleevelike manner. He wrote that between the membrane and the capillary wall there is a space "filled with colorless granular fluid, and in people above 40 or 45 years of age with fatty granules and abundantly with an amorphous hematein." Robin, while not assigning any special rôle to this space, believed it to be of importance in physiologic and pathologic conditions. Virchow[5] also noted similar perivascular spaces "which are very expansible, forming sometimes sack-like outpocketings filled with water or with blood." Like Robin, Virchow did not attribute any definite function to these spaces. Subsequently, the latter were interpreted as lymphatics and designated as "lymphatic spaces of Virchow-Robin" (Virchow-Robinsche Lymphräume).

The lymphatic spaces described by His[6] differ from those of Virchow-Robin in that they are outside of the latter. His, by injecting mercury into the subpial

4. Robin, C.: Recherches sur quelques particularités de la structure des capillaires de l'encéphale, J. physiol. **2**:537, 1859.

5. Virchow, R.: Ueber die Erweiterung kleineren Gefässe, Virchows Arch. f. path. Anat. **3**:425, 1851.

6. His, W.: Ueber ein perivasculäres Canalsystem in den nervösen Centralorganen und über dessen Beziehungen zum Lymphsystem, Ztschr. f. wissensch. Zool. **15**:127, 1865.

spaces, found that the metal passed down into the brain by way of channels the inner wall of which was the membrane described by Robin and the outer an independent second sheath that touched the cerebral substance. More recent writers stated that the cerebral blood vessels are invested with two membranes; one is that of the pia, which follows the cerebral blood vessel after it has left the pia-arachnoid; the other is the glial membrana limitans, which separates the brain from the mesenchyme. The Virchow-Robin lymphatics are believed, then, to lie between the pial membrane and the wall of the blood vessel, while those of His are between the glial limiting membrane and that of the pia.

Subsequent investigations have convincingly shown that the lymphatics noted by His were artefacts due to injections of the heavy metal. Moreover, the lymphatic spaces of Virchow-Robin are artificial formations and owe their existence, as do the spaces of His, to injections of material from outside or probably to pathologic factors. Robin himself, in a later publication, reported having seen similar perivascular spaces also in the omentum.

Held[7] stated that spaces in the central nervous system "acting as lymphatics" are present not outside but within the blood vessel wall, i. e., between the media and the adventitia; while Spielmeyer[8] was of the opinion that the entire vascular coat is made up of "lymphatic spaces." The adventitia of the cerebral blood vessels when treated with silver tannin discloses, according to this author, a fine reticular structure composed of intercommunicating compartments, which are particularly conspicuous in disease conditions like sleeping sickness. The German workers have designated these so-called lymphatics as "adventitial spaces of Virchow-Robin" (Virchow-Robinsche adventitielle Lymphräume).

In the cerebral blood vessels, as in the visceral, one notices the customary fenestration (membrana fenestrata) and also the vasa vasorum. In some pathologic processes, the latter increase in number and dilate forming spaces of various size which may be interpreted as lymph channels. It would appear that lymphatics as seen at the periphery of the body are lacking in the central nervous system.

The "body fluid" of the central nervous system is the cerebrospinal fluid, extracted from the blood and filtered or possibly secreted by the choroid plexus (called by some investigators "choroid plexus gland"). From the latter through the foramen of Monro, the third ventricle, the aqueduct of Sylvius and the fourth ventricle and thence via the foramina, it reaches the subarachnoid spaces, where it is absorbed. The absorption is believed to be effected by way of the arachnoid villi into the great sagittal sinus, and by way of the perineural spaces, the latter being defined as an accessory drainage. The perineural spaces convey the fluid to the tissue spaces and through the intervention of the latter it is taken up by the cervical lymphatics (Weed[9]).

In a study of a cerebral metastasis from a carcinoma of the breast, Hassin[10] believed that the tumor reached the meninges via the perineural spaces in the following manner: From the periphery, the new

7. Held, H.: Ueber die Neuroglia marginalis der menschlichen Grosshirnrinde, Monatschr. f. Psychiat. **26**:360, 1909.

8. Spielmeyer, W.: Histopathologie des Nerven-Systems, Berlin, Julius Springer, 1922.

9. Weed, L. H.: Studies on the Cerebrospinal Fluid and Its Pathway, J. M. Research **31**:21 (Sept.) 1914; Am. J. Anat. **31**:191 (Jan.) 1923.

10. Hassin, G.: Histopathology of Carcinoma of the Cerebral Meninges, Arch. Neurol. & Psychiat. **1**:705 (June) 1919.

growth reached the lymphatics of the neck and thence, via the tissue spaces, the perineural spaces "climbing" upstream to the meninges and finally reaching the brain. Other writers described the same pathway for bronchiogenic cancer.

At the present time there is a general agreement that cancer metastasizes to distant organs by way of every possible channel. Letulle and Jacquelin [11] produced evidence to show that the transmission of tumor from one lung to the other was effected by way of the bronchi ("métastase aèrienne"). Goldmann [12] affirmed that mammary cancer is often propagated by way of the lactiferous ducts. The transmission of a carcinoma via the lymphatics, held by the older pathologists as being the essential pathway for the spread of an epithelial malignant disease, was stressed in recent years by Handley,[13] who produced evidence to show that it is effected in two ways: (1) by permeation and (2) by transportation (cell emboli). In the first instance, tumor cells reaching the lymph vessel continue to grow within its lumen "conquering new territory" step by step. "Their driving force is an internal pressure resulting from their own proliferation," and as a rule they follow the lymph stream (othograd "infection"). "Cancer thus spreads," said Handley, "by permeating the lymphatic system like an invisible annular ringworm." In cases in which the lymphatic channel is blocked by fibrosis or by pressure from outside, cancerous cells continue their proliferation against the lymph stream (retrograd "infection").

In the material studied by us, the bronchiogenic cancer, in all probability, reached the central nervous system by way of the blood stream.

That cancer cells are frequently present in the pulmonary vessels forming emboli therein without invading the vessel wall was noted years ago by Schmidt.[14] This author also found tumor cells in the lumen of capillaries and veins, where they proliferated.

In our own investigation, tumor cells were invariably found in the lumen and walls of the blood vessels of every organ studied. The constancy of this phenomenon makes us believe that the hematogenous manner of dissemination of bronchial carcinoma is the essential one.

Goldmann showed that in experimental cancer the blood vessels undergo early pathologic changes. This is particularly marked in the veins, which show degenerative changes at the beginning of the disease.

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11. Letulle, M., and Jacquelin: Les "embolies bronchiques" cancéreuse, Presse méd. **32**:825, 1924.

12. Goldmann, E. E.: Studien zur Biologie der bösartigen Neubildungen, Beitr. z. klin. Chir. **72**:1, 1911.

13. Handley, W. S.: Cancer of the Breast, New York, Paul B. Hoeber, 1922.

14. Schmidt, M. B.: Verbreitungswege der Carcinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903.

The arteries resist damage for a longer time; and, as in inflammatory conditions of bacterial or toxic origin, they play for some period of time the rôle of "insulators."

Neoplastic cells aggressively invade the vascular coat, being disseminated throughout the vessel wall by way of the vasa vasorum. This is suggested by the fact that in the arteries in which nutrient vessels are particularly prominent in the outer coats, the tumor is essentially "periarterial," while in the thin-walled veins, the new growth is seen

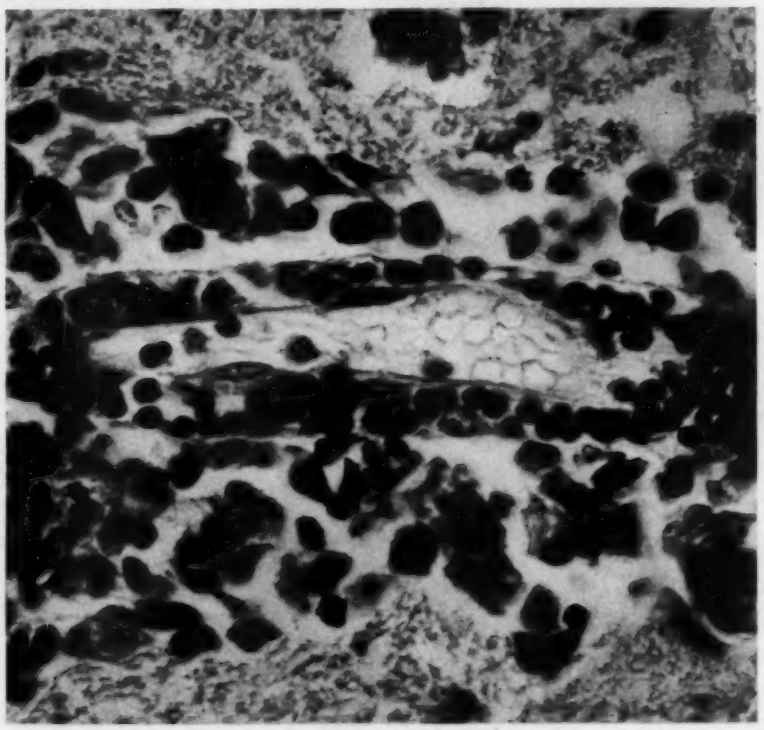

Fig. 1.—Dissociation of the vessel wall by lymphocytes from the blood stream with no evidence of lymphatic spaces in the vascular coat, in a case of sarcomatosis of the brain. Hematoxylin and eosin; × 300.

as an endophlebitis. Thus, an endophlebitis carcinomatosa is shown in figure 3, in which the cells lying free in the lumen reveal multiple mitoses. A thrombosis of a pulmonary vein by cells of a bronchiogenic cancer is demonstrated in figure 4, in which the invasion of the vascular coats by carcinomatous cells is also conspicious. Organization of a carcinomatous thrombosis is seen in figure 5. This illustration also shows the presence of carcinomatous cells in the vascular coat and in the distended vasa vasorum. In the insert is a photomicrograph of a

thrombosed and "canalized" pulmonary vein. The canaliculi are lined by malignant epithelial cells. In such a position, neoplastic cells may remain for an indefinite period, until they ultimately reach a larger blood vessel, which they invade and thus metastasize to distant organs. The occurrence of late metastases is probably often due to a condition in which the cells are thus immured without being destroyed. The presence of cancer cells in cerebral vessels is illustrated in figures 6 and

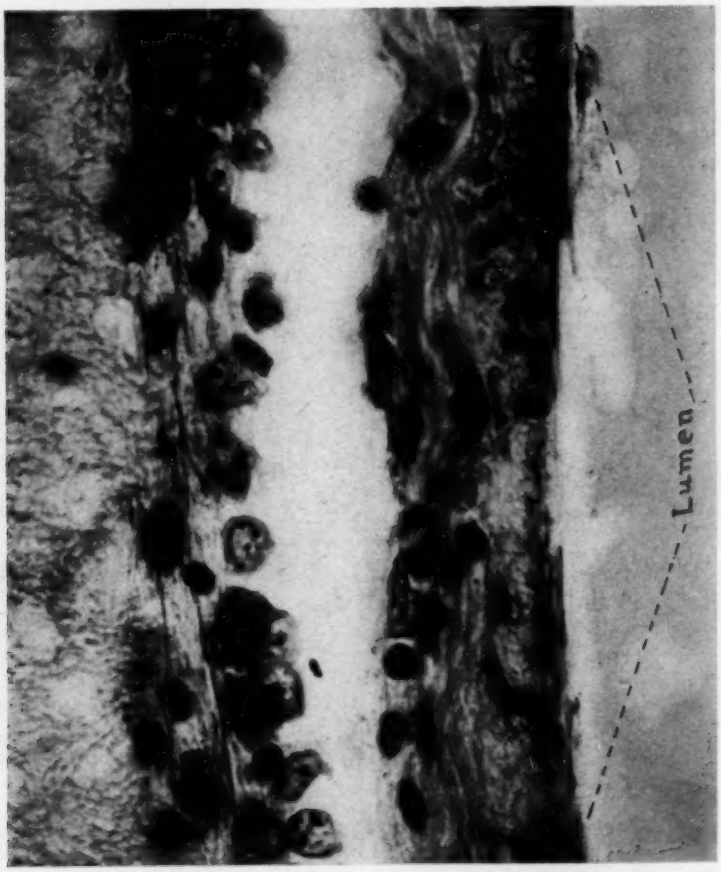

Fig. 2.—Splitting of the vessel wall by invading neoplastic cells in a case of sarcomatosis of the brain. Again there are no adventitial or lymphatic spaces in the vascular coat. Eosin-methylene blue; × 850.

7. Here, too, the lumen and the walls of the vessels are shown invaded by malignant cells. Finally, the distention of a few nutrient vessels by tumor cells is beautifully illustrated in figure 7.

The fact that in most instances the brain contained numerous tumor nodules invading practically every part of the hemisphere and also

the cerebellum is further evidence for the hematogenous transport of "showers" of emboli to various parts of the brain.

Hematogenous metastases apparently occur either through the transmission of a single cell or a minute clump of cells or through the formation of actual tumor emboli. In both instances, as stated, secondary tumors arise that grow inside the vessels and also, by crossing the vessel wall, in the surrounding tissue.

The rather frequent occurrence of cerebral metastases in primary carcinoma of the lungs, an occurrence which is much rarer in extra-

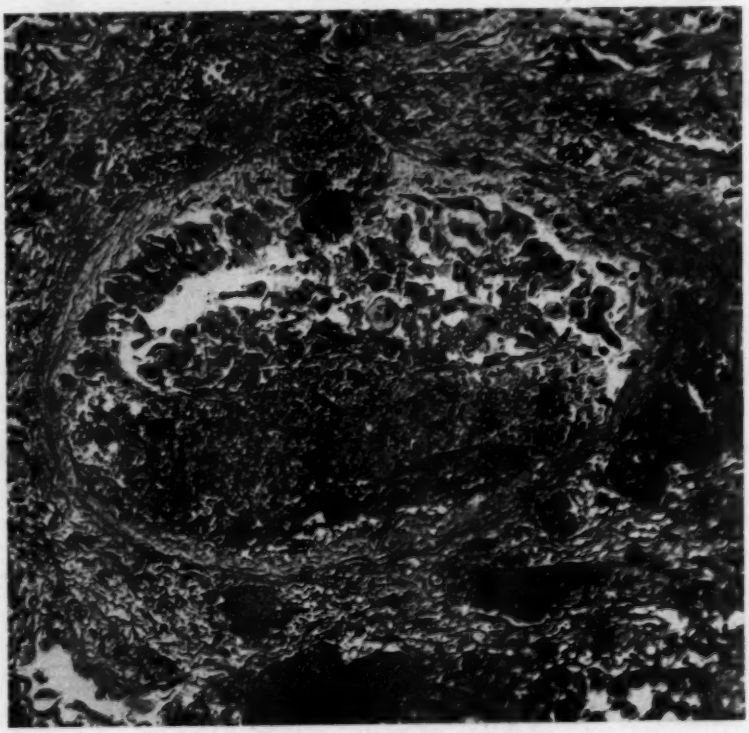

Fig. 3.—A section of a pulmonary vein partly occluded by a neoplastic thrombus from a bronchiogenic cancer. There is beginning organization of a thrombus of the blood cells. Eosin-methylene blue; × 175.

pulmonary cancer, is favored not only by the aforementioned factor, but by the absence of any barrier between the lungs and the brain. A cell embolus from a pulmonary cancer, as is clearly understood, may pass from the pulmonary vein and heart directly into the general and then into the cerebral circulation. A similar embolus from elsewhere in the body on its way to the central nervous system passes primarily through the "sieve" of the lungs, the latter serving as a barricade, thus

keeping back the advance of the growth. Visceral cancers reach the lungs with great frequency. The tumor emboli are retained, however, by the pulmonary capillaries in which they are immured. Moreover, frequently they lead to local infarct formation followed by organization and destruction of the metastatic neoplastic cells.

It is interesting that a pulmonary abscess is more often complicated by a "metastatic" cerebral abscess than are abscesses of other organs. It is likely, then, that the frequent occurrence of metastases to the brain from a pulmonary abscess and a pulmonary carcinoma is not a mere coincidence, but is due to the same underlying factor; that is, a

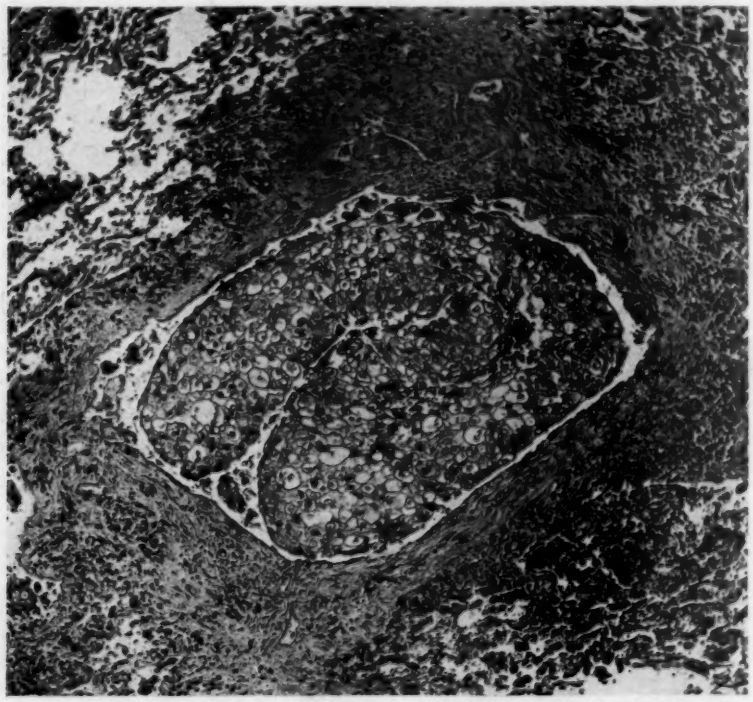

Fig. 4.—A section through a pulmonary vessel thrombosed by neoplastic cells in bronchiogenic cancer. Tumor cells are also seen in the wall of the blood vessel. methylene blue-eosin; × 80.

hematogenous transmission to the brain of a "pus embolus" analogous to the transmission of a carcinomatous "cell embolus."

MATERIAL AND TECHNIC

The material consisted of eleven brains and ten specimens removed at operative exploration. In four instances, the surgical material only was available for study, while in the other, both material obtained at operation and tissues obtained at necropsy were studied.

Tissues were fixed in a 10 per cent solution of formaldehyde and also in Zenker's fluid.

Paraffin sections were stained with hematoxylin and eosin, with methylene blue and eosin and also with phosphotungstic acid and hematoxylin. Frozen sections were studied with Bielschowsky's silver nitrate method, with Penfield's[15] combination method for microglia and oligodendroglia and also with the gold chloride sublimate method as modified for formaldehyde-fixed tissue by Globus.[16]

REPORT OF CASES

CASE 1.—*Sudden onset with numbness and tingling of left arm. Jacksonian attacks and loss of memory. Cerebral exploration with removal of tumor. Microscopic diagnosis: carcinoma, probably metastatic from the lung.*

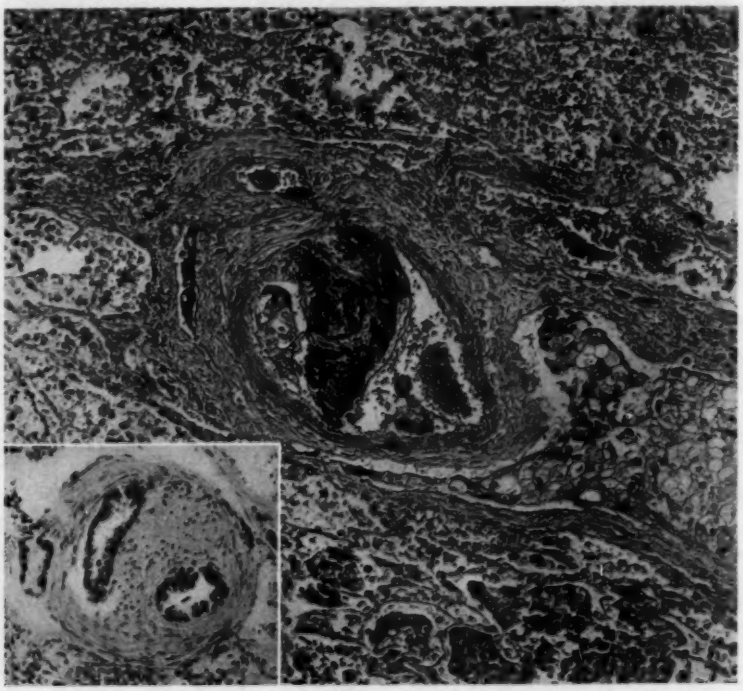

Fig. 5.—A section through an organized neoplastic thrombus in a pulmonary vessel. Tumor cells are also present in the vasa vasorum. The insert shows the canaliculi of a thrombosed pulmonary vessel, lined by tumor cells. Eosin-methylene blue; × 80.

History.—On March 18, 1927, a Canadian physician, aged 67, was referred for observation by Dr. John Stewart of Halifax, Nova Scotia. The symptoms of the illness began suddenly three months before admission when the patient felt his

15. Penfield, W.: A Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. **4**:153, 1928.

16. Globus, J. H.: The Cajal and Hortega Glia Staining Method: A New Step in the Preparation of Formaldehyde-Fixed Material, Arch. Neurol. & Psychiat. **18**:263 (Aug.) 1927.

left arm become numb and tingle. One week later, twitching of the muscles of the left hand, arm, leg and left side of the face occurred and lasted for several minutes. These attacks recurred repeatedly. Soon he began to drag his left leg and had severe headaches. This was followed by loss of memory and by periods of disorientation. There were no general pressure symptoms.

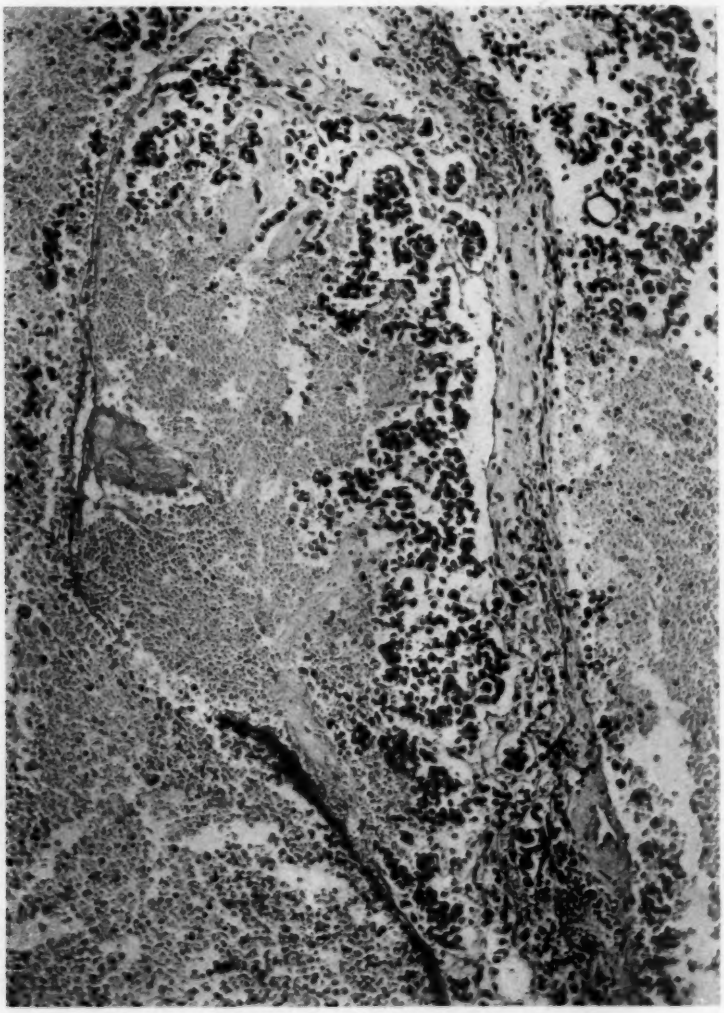

Fig. 6.—Invasion of wall of a cerebral vessel and thrombosis by metastatic cells from a bronchiogenic carcinoma. Tumor cells are seen in the vasa vasorum. There also is necrosis of the vessel wall. Hematoxylin and eosin; × 110.

Physical Examination.—There was a weakness of the left side, a weakness of the lower part of the left side of the face, astereognosis of the left hand and a failure of memory. Although there was no choking of the optic disks on admission, there was a choking of over 2 diopters before the operation. An intracranial tumor was suspected and an exploration performed.

Course of Illness.—On March 30, 1927, Dr. Cushing removed a nodule from the upper portion of the right postcentral convolution. The histologic sections showed a carcinoma, probably of pulmonary origin. The roentgen films of the lung were interpreted as showing no tumor. The patient was discharged improved on April 8, 1927. He continued to improve and regained much of his former activity for about the next eighteen months, and then in September, 1928, he began to fail again. In the next six months there was a gradual failure, until death occurred on April 7, 1929, almost two years from the date of his operation and about thirty months from the onset of his illness. The brain was removed

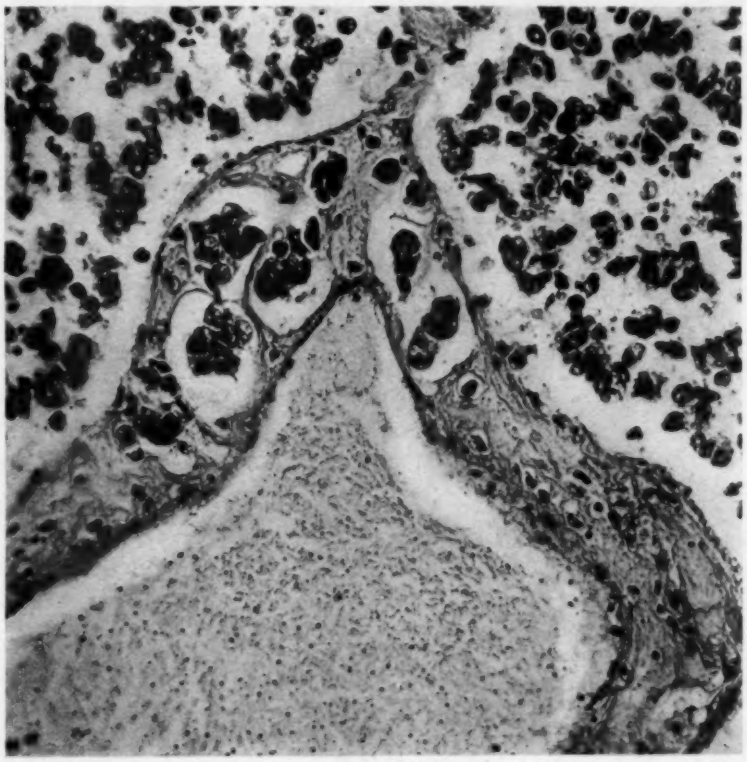

Fig. 7.—A section of a cerebral blood vessel showing neoplastic cells from a bronchiogenic carcinoma in the vasa vasorum. Hematoxylin and eosin; × 300.

by Dr. R. P. Smith of Halifax, Nova Scotia, and sent to this department for examination.

Brain.—A series of thin coronal sections demonstrated three large typical metastases (fig. 8). Two were symmetrically located in the posterior part of the frontal lobes just below the corpus callosum, each measuring 1.5 cm. in diameter. At the site of the previous operation was a large metastasis 5 cm. in diameter. All these nodules were well demarcated and appeared enucleable. Their centers were opaque and necrotic, while the borders consisted of pinkish-red, translucent, tumor tissue.

The meninges did not appear unusual.

Microscopic Examination.—The sections of the specimen taken at operation showed a malignant epithelial tumor resembling other examples of metastasis from cancer of the lungs. The cells were columnar, forming acini with papillary projections, lined by neoplastic cells. The sections through the recurrent metastatic nodule at the site of the operation showed a dense gliosis in the adjoining brain substance. There was also a marked response on the part of the macrophages (fig. 9).

Comment.—The death of this patient occurred as the result of the multiple metastases to the brain with the consequent high degree

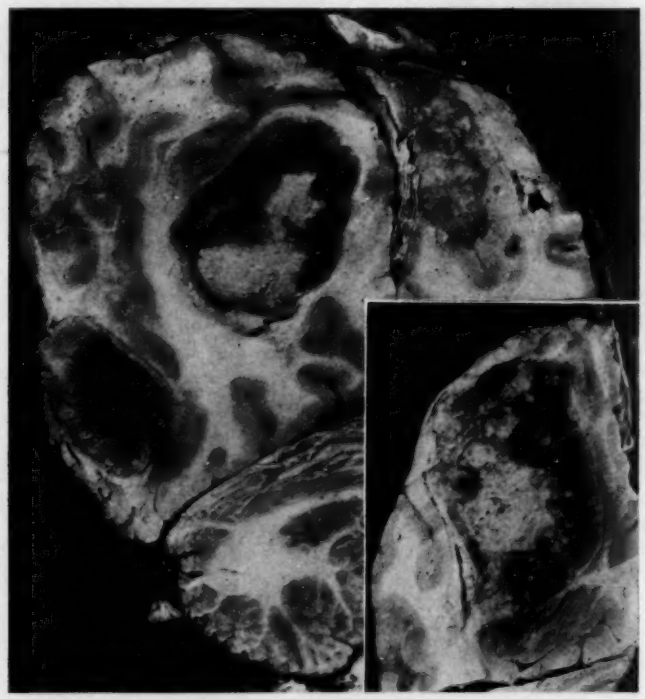

Fig. 8 (case 1).—Metastases to the brain from a primary carcinoma of the lung. The insert shows a section through the old operative site to show the recurrence of a metastasis two and one-half years after the operation. The center of each nodule is necrotic. The brain was distorted in transportation.

of intracranial pressure. One of the interesting features of this case is the fact that there were no known symptoms of a pulmonary lesion during the relatively long survival period.

The roentgenogram of the skull was interpreted as showing some porosity of the cranium over the suspected site of tumor, and from these observations a meningioma was believed to be present. The sudden onset of symptoms suggested either a cerebral vascular lesion or a cerebral metastasis. The further course of the illness, with the

gradually increasing papilledema, made it certain that an intracranial tumor was present. There was no evidence of a primary tumor elsewhere. The first roentgenograms of the thorax were interpreted as showing no definite evidence of a tumor, although there were shadows at the hilum of the right lung. At a reexamination of the films it was suggested, however, that the roentgenologic aspect of the chest was compatible with a primary carcinoma of the lungs.

CASE 2.—*Onset with general weakness, cramps in legs, unsteadiness of feet, headaches; left spastic hemiplegia and extreme choking of optic disks. Cerebral*

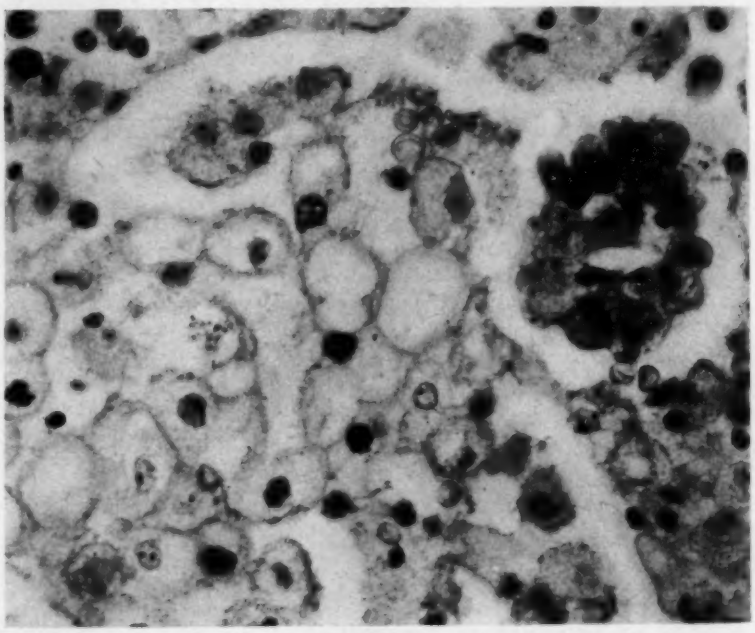

Fig. 9 (case 1).—Macrophage reaction at the periphery of a metastatic nodule. Eosin-methylene blue; × 600.

tumor suspect. Operation with removal of tumor. Death. Postmortem finding of primary carcinoma of bronchus with metastases to the brain.

History.—On April 22, 1927, Joseph D., aged 44, was referred by Dr. R. Wood of New Bedford, Mass. The present illness began four months before admission with general weakness, cramps in the legs and vague pains throughout the body. A diagnosis of rheumatism was made, and a tonsillectomy was performed. The patient had a severe postoperative hemorrhage. Shortly after the operation, he became unsteady on his feet, had severe headaches and was incontinent of urine.

Physical Examination.—The patient was disoriented, speechless and incapacitated by a left spastic hemiplegia. Both optic disks were swollen with scar tissue and hemorrhages, denoting that the papilledema had been present for some time.

Course of Illness.—It was the impression that a tumor was present in the right precentral region. Two days after admission, he had a slight hemoptysis, cough-

ing up blood-streaked mucus. The results of an examination of the lungs were considered as normal.

On April 28, 1927, a right cerebral exploration was made by Dr. Cushing and what was considered in the gross and by immediate microscopic examination as a meningioma was removed from the right precentral area. The patient died twenty-four hours after the operation.

Necropsy.—The body was well nourished. There was a primary carcinoma of the bronchus to the right upper lobe with almost complete occlusion of this bronchus and contraction of the pulmonary artery to the right upper lobe. Metastases were found in adjacent bronchial lymph nodes, in the right kidney and in the brain.

Brain: The entire superior longitudinal sinus was occluded by a recent thrombus. A number of coronal sections showed an unusual edema of the entire brain and but one degenerated metastatic nodule in the tip of the left frontal lobe.

Microscopic Description.—Lungs: The cells were cuboidal and arranged in alveoli with frequent tufting of the cells, so that they projected into the lumen from three to four cells in height. The blood vessels and the lymph vessels were invaded by the tumor. One large lymph node was replaced by tumor, and a section of a nerve showed that it, too, was invaded by tumor.

Brain and Meninges: There was an infected thrombus filling the superior longitudinal sinus. There was much necrosis of the brain elsewhere than near the metastases. The metastases were necrotic, and living cells were seen best at the periphery, where they formed collars about all the vessels. The response of the fibrous astrocytes, clasmatodendrosis of some of these cells, the changing of microglia into phagocytic cells and the swelling of the oligodendroglia were followed in the selectively stained sections.

Comment.—Here is another example of the difficulty of clinical diagnosis of this type of lesion in the central nervous system.

The choking of the optic disks apparently occurred early in the course of the disease, as the scar tissue formation indicated. The hemoptysis two days before the operation was not investigated and no roentgen examination of the chest was made. At the operation, Dr. Cushing remarked about the pronounced cerebral edema and the presence of an unusual tumor embedded in the cerebrum. At the immediate investigation of the operative specimen, it was thought that it was a meningioma. The finding of a bronchiogenic carcinoma of the right upper lobe was a complete surprise.

The clinical history of this patient bears a close resemblance to that of the patient in case 1. In each case, the interval from the onset of symptoms to operation was short, and in each instance a tumor was removed from the right motor area. In case 1, however, there was late choking of the optic disks and little cerebral edema; in this case, there was advanced choking of the optic disks and great edema. Possibly because of that, this patient died soon following the operation, while the patient in case 1 lived for over two years after the cerebral exploration.

CASE 3.—*Sudden onset with headaches, unconsciousness, convulsions; early signs of intracranial pressure. Dysarthria. Drowsiness. Cerebral tumor suspected. Right occipital exploration with finding of two enucleable tumor nodules. Pathologic diagnosis: metastatic cancer. Death two months later. Necropsy.*

History.—On Sept. 30, 1927, George J., a Lithuanian, a railroad yard worker, aged 49, was referred by Dr. E. L. Hunt of Worcester, Mass., with a diagnosis of tumor of the brain. Two and one-half years before admission, he was operated on for a gastric ulcer. The present illness began suddenly three months before admission with a severe headache. He went to bed, but had a generalized convulsion four hours later. On regaining consciousness, he had a most severe frontal and occipital headache. Within the next three days, he had had three similar attacks. Dizziness began shortly afterward and continued until the admission. In the month before admission, he developed tinnitus in the right ear, dysarthria, dimness of vision and projectile vomiting.

Physical Examination.—The patient was well nourished. There was a swelling of both optic disks of from 3 to 4 diopters. A slight weakness of the left side of the face was noted during the periods of examination. The patient was drowsy. The roentgenogram of the skull was interpreted as showing a tumor in the right hemisphere, for areas of calcification were shown posterior to and above the pineal gland.

Course of Illness.—Localizing signs of a tumor were absent; therefore, in order to save vision, a right subtemporal decompression was made. The patient was somewhat relieved by this procedure and was discharged on Oct. 24, 1927. Soon the severe headaches recurred, and he returned to the hospital on Nov. 10, 1927.

On Nov. 18, 1927, a right occipital exploration was made by Dr. Horrax, and encapsulated, hard tumors which resembled metastatic lesions were removed. The immediate examination of this tissue showed it to be a metastatic adenocarcinoma the primary origin of which was undetermined. On the day before discharge, Dec. 3, 1927, the only roentgenogram of the lungs made was interpreted as showing a small area of consolidation in the upper right middle lobe, "probably an incompletely resolved pneumonia."

There was temporary improvement after the operation, but soon a recurrence of the previous symptoms caused a gradual decline, with death occurring on April 29, 1928, about nine months from the onset of the symptoms of an intracranial lesion. A complete necropsy was made at the Worcester City Hospital, and the organs were forwarded here for examination.

Necropsy.—The body was well nourished. An adenocarcinoma of a bronchus with metastases to the suprarenal glands, kidneys and brain was found. The tumor originated in the bronchus to the right upper lobe and had metastatsized to the adjacent bronchial lymph nodes. In the kidneys and suprarenal glands there were single, encapsulated, firm, metastatic nodules.

Description of Specimens.—The two metastatic nodules removed at operation from the right parietal and temporal lobes were reddish-gray and enucleable, and measured 3 and 1 cm. in diameter, respectively.

The brain was edematous, with flattened convolutions. Innumerable metastases were scattered in every portion of the brain. At least 100 nodules ranging from a few millimeters to 2 cm. in diameter were seen in the thin coronal sections of the entire brain. All these nodules were firm and grayish-red and showed little necrosis in the gross.

Lungs: The primary tumor was made up of columnar cells arranged in alveolar form. There was a tremendous increase in the connective tissue in which collections of tumor cells appeared to be isolated. The only invasive portion of the tumor was beneath the bronchus, and here the cartilage and entire wall were invaded by tumor cells. Frequently, tumor cells were found in the lumen of blood vessels.

Brain: The tumor cells in each of the metastatic nodules appeared much more malignant than the cells of the primary tumor. They were columnar and cuboidal and each had a deep, irregular, hyperchromatic nucleus. They were often piled up in layers from two to four cells deep. Frequently, groups of large, single cells with enormous, irregular, deep blue-staining nuclei invaded the brain. As in previous cases there was some response on the part of the fibrillary astrocytes and the microglia.

Comment.—The sudden onset with headache and convulsions ushered in the clinical symptoms of an intracranial lesion. There were no symptoms or clinical observations of the bronchiogenic tumor. As in many cases in which metastatic cerebral lesions are present, the localizing signs were so indefinite as to warrant, at first, only a subtemporal decompression. The general pressure symptoms with a high degree of papilledema were noticeable early. They were associated with the extreme edema of the brain rather than with a hydrocephalus.

The results of the necropsy need but little comment. The small primary tumor which had invaded many lymphatics and adjacent small blood vessels was typical of carcinoma of the bronchus. The metastases duplicated the histologic structure of the primary tumor.

It is noteworthy that the results of a roentgenologic examination performed about five months before the patient's death were interpreted as showing an unresolved pneumomic process and not a new growth.

CASE 4.—*Sudden onset of cerebral symptoms in 1919 with weakness and paralysis of right side. Early choking of optic disks. Subtemporal decompression (elsewhere). In 1920, at a cerebral exploration a necrotic, infiltrating tumor was removed. Pathologic diagnosis: carcinoma. Death at home. No necropsy.*

History.—On May 31, 1920, James H., an American farmer, aged 41, was referred by Dr. J. Higgenbotham of Sunken Gardens, Va., with a diagnosis of tumor of the brain. The patient had always been well, except for influenza about six months before the onset of his present illness. A chronic nonproductive cough followed, and a diagnosis of pulmonary tuberculosis was made, but never verified. The onset of the cerebral symptoms occurred suddenly four months before admission. At that time he fell off his porch, and when picked up was found to have a weakness of the right foot. Soon the entire right side was weak, and the signs of increased intracranial pressure were apparent in dimness of vision, headaches and vomiting. A subtemporal decompression was made, but it was followed by only temporary relief.

Physical Examination.—The patient was emaciated. There was a paralysis of the entire right side, and also a motor and sensory aphasia. The optic disks were swollen.

Course of Illness.—On June 9, 1920, Dr. Cushing made a left osteoplastic exploration and partially removed a cystic tumor from the left hemisphere. The

cyst content was mucoid, and a direct smear revealed cocci and bacilli, although a culture of the same material showed no growth. The microscopic sections of the tumor were interpreted as showing a papillary adenocarcinoma, probably of the choroid plexus.

On June 26, 1920, shortly before discharge, a roentgen examination of the chest was made. The chest was asymmetrical with the mediastinum displaced to the left side and an increase in the shadows of the left hilum and posterior mediastinum at the level of the bifurcation of the trachea, interpreted as a mediastinal tumor.

The patient returned home, and died on Sept. 8, 1920, about seven months from the onset of the cerebral symptoms. Necropsy was not allowed.

Description of Specimen Obtained at Operation.—A collapsed cystic structure with masses of grayish-white tumor attached represented the specimen. The mucoid material adhered to the thin-walled cystic portion.

Microscopic Examination.—The tumor cells were all of the tall columnar type arranged in small cysts and glandlike structures into which there were papillary projections of the tumor. Mitoses were commonly found and when present the cells were distorted and appeared polygonal in shape. The cells did not tend to invade the brain either directly or along the walls of the blood vessels. Moderate gliosis was present in the adjacent cerebral tissue.

Comment.—Although the tumor in this case was an adenocarcinoma, no one ever thought that its primary source might well be in the lungs. The roentgenologic examination of the chest was performed because pulmonary tuberculosis was suspected, and the finding of a new growth characteristic of a bronchiogenic tumor was a surprise. The decompression effect of the cerebral exploration relieved the patient's symptoms for a few months.

CASE 5.—*Onset in 1922, with right hemiplegia and aphasia. Cerebral tumor suspected. Exploration, with removal of malignant epithelial tumor from left motor area; primary source unknown. Recurrence of symptoms six months later. Second exploration. Complete recovery. In 1928, discovery by roentgen examination of a carcinoma of the lungs. Death. Necropsy not allowed.*

History.—On Nov. 14, 1928, Henry S., a Russian Jew, aged 70, was admitted to the medical service for observation. He had previously been in the surgical service three separate times, following December, 1922, for two intracranial operations and for the repair of a hernia. The onset of the illness in question occurred about July, 1922, with the gradual development of paralysis of the right arm and leg and apraxia.[17] On examination, the optic disks showed a choking of 2 diopters, and there was a spastic hemiplegia on the right. A diagnosis of tumor of the left motor area was made, and an enucleable tumor, weighing 85 Gm., was readily removed from that region on Dec. 22, 1922.

The patient was discharged three weeks later free from symptoms.

Six months later there was a recurrence of the symptoms, and at a second operation a tumor weighing 45 Gm. was enucleated from the same site as the first tumor. Three weeks later, the patient was discharged, entirely free from symptoms.

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17. This aspect of the case was investigated by Bailey, P.: A Contribution to the Study of Aphasia and Apraxia, Arch. Neurol. & Psychiat. **11**:501 (May) 1924.

He was reexamined in December, 1925, and found to be normal, and indeed he lived a normal life until Sept. 4, 1928; then a right femoral hernia became incarcerated. While the patient was in the hospital for repair of the hernia, a study was made to find out the source of the metastatic cerebral lesion removed six years before. The gastro-intestinal tract, the genito-urinary tract, the prostate and the skin were ruled out by study. Signs of localized impaired resonance and abnormal breath sounds in the left upper lobe were found. Stereoroentgenograms of the lungs showed a soft shadow in the left upper lobe corresponding to the pathologic area found in the clinic.

Following this admission, the patient coughed up blood-streaked sputum which showed no tubercle bacilli or abnormal cells.

Within a short time after his discharge, the patient began to lose weight, began to have a productive cough and had severe pain in the intercostal regions and the right arm. He was then readmitted to the hospital, to the medical service, where clinical evidence of diffuse involvement of the lungs was confirmed by the roentgen examinations. Apparently there were also metastases to many of the bones.

He died on Nov. 22, 1928, about seven years after the onset of the cerebral symptoms. Necropsy was not permitted.

Microscopic Examination.—Brain: Sections of the separate metastatic nodules removed at operation in 1923 were available for study. Previous to the clinical demonstration in 1928 of the evidence of a carcinoma of the lung, various diagnoses were made from these slides. Areas suggesting either a chordoma or a metastatic "hypernephroma" were described.

After having studied a large number of sections of metastatic lesions of the brain, especially of metastases from tumors of the lungs, we are convinced that the cells of this tumor were epithelial in origin and in all probability came from a primary tumor of the lung. There was an abundance of necrosis, but where the tumor cells were better preserved they grouped themselves in alveolar arrangement with multiple papillary projections into the lumen. The cells were high cuboidal, were without cilia and had deep black, irregular nuclei. There was little reaction to be seen in the small portion of the attached brain tissue. When the tumor cells were necrotic, they appeared huge and rounded or polygonal with small eccentric nuclei and an abundance of cytoplasm.

Comment.—The patient was studied thoroughly by the members of the surgical and medical staffs of the hospital. It appeared beyond any reasonable doubt that the secondary epithelial growth removed from the brain in 1922 had metastasized from the lungs; at that time, the pulmonary lesion was probably in the early stage of its development. The patient survived more than six years after the removal of the metastatic nodule. This case again is of interest in connection with the advisability of intracranial exploration, which we shall take up in the general comment. It also shows that bronchiogenic cancer, as probably do most cancers, grows slowly, particularly in persons of advanced age.

CASE 6.—*Gradual onset with headaches, loss of strength and loss of vision. Weakness of the right side of the face. Osteoplastic exploration with removal of large cystic tumor. Histologic diagnosis: metastatic epithelial tumor. Recurrence of symptoms followed by a second operation twenty months later with removal of a large cyst. Recovery. Sudden death from pulmonary embolus two weeks after operation.*

History.—On April 6, 1925, Mrs. G., a Jewish housewife, aged 46, was admitted to the medical service of this hospital with the complaint of headaches. The onset of the illness five months before admission was sudden with severe headaches. Soon there was a gradual loss of vision and of strength.

Physical Examination.—There was evidence of a slight loss of weight. Weakness of the right side of the face and bilateral choking of the optic disks were the only other positive observations.

Course of Illness.—The patient was considered as having a tumor of the brain and was transferred to the surgical service. A ventriculogram demonstrated a block of the left foramen of Monro and a multicystic tumor in the left occipital lobe.

On April 25, 1925, Dr. Cushing performed a left occipital exploration and removed a cystic tumor. The fluid in the cyst was mucoid and yellow, and contained cholesterol crystals, fat and macrophages.

The microscopic sections showed a carcinoma, probably of bronchiogenic origin.

The chest was then examined by the roentgen rays and revealed a tumor in the hilum of the left lung.

The patient made an uneventful recovery and was discharged improved.

The patient was seen at intervals during the next two years. One year after the operation, there was distinct clinical evidence of a cerebral embolus the effects of which gradually wore off. At times, there was some evidence of pleurisy on the left side and occasional hoarseness.

On Feb. 18, 1928, symptoms of intracranial pressure recurred, and the patient was readmitted to the hospital. Roentgen examination of the lungs made then showed in the left hilum a shadow which was somewhat increased in size as compared with that seen at the first examination. A careful search for a neoplasm elsewhere in the body revealed none.

A second exploratory operation was then performed on Feb. 28, 1928, and a cystic tumor was removed from the same location as the previous tumor (fig. 10).

The patient was making a normal recovery when death occurred suddenly on March 6, 1928, about three years from the onset of the cerebral symptoms. Necropsy was not permitted.

Description of Specimens.—The first specimen removed in 1925 from the left occipital lobe consisted of a multilocular cystic mass about 5 cm. in diameter. It contained over 30 cc. of dirty, orange fluid, the examination of which disclosed macrophages, cell débris and many cholesterol crystals. The wall was thin, and local thickenings of grayish-white tissue represented mural nodules of tumor.

The second specimen (fig. 10), removed in 1928 from the same location as the first cyst just described, consisted of a large, oval cyst, measuring after fixation 9 by 6 cm. and containing more than 75 cc. of a material similar to that found in the first specimen. This large cyst had a thin, transparent wall and contained one large mural mass of grayish-white tissue about 3 cm. in diameter and 2 cm. in height. This tissue was partially necrotic and resembled both the tissue from an early primary tumor of a bronchus and other metastases to the brain in this group.

Sections of the metastasis removed in 1925 and in 1928 were available for study. There was an abundance of mucoid material and crystals. The tumor cells in both specimens were low cuboidal cells arranged in thick strands or alveoli. There were relatively few mitoses. The nuclei were less hyperchromatic, and the cells appeared smaller in the specimen removed in 1925 as compared with the last

specimen. In the first specimen there would be some doubt as to the origin of the primary tumor. However, in the second specimen the cells resembled those observed in several other cases of this series in which the presence of primary tumor of the lung was confirmed by necropsy.

Comment.—When the histologic examination of the cerebral tumor revealed a carcinoma the attention of the staff was directed to the visceral organs in order to locate the primary source of the disease. In addition to the roentgenologic examination of the gastro-intestinal tract and of the genito-urinary organs a roentgenogram was taken of the chest. It revealed the presence of the primary new growth.

The records of the Peter Bent Brigham Hospital show that from 1913, the year of the foundation of the hospital, to 1925, a certain

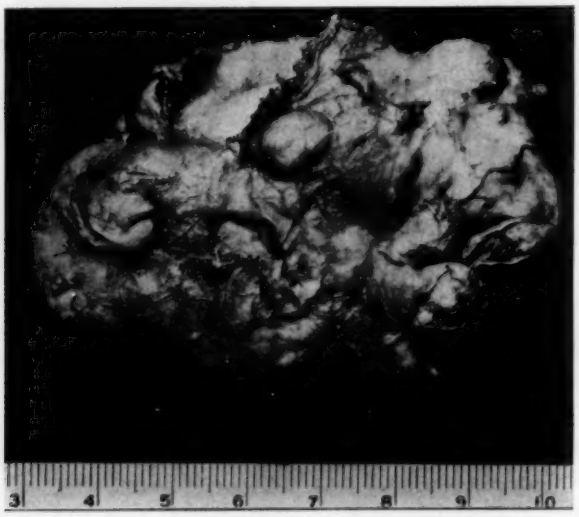

Fig. 10 (case 6).—A cystic metastatic tumor from a primary tumor of the lung, removed at a second operation performed two years after the first operation.

number of patients with histories similar to those recorded here were under observation in the clinics. After the nature of the cerebral lesion was disclosed, investigation was usually directed to every visceral organ except the lungs, and the patients were discharged with the diagnosis of carcinoma, metastatic to the brain, primary source unknown. Since it became apparent that the brain is the common site of metastases from primary tumors of the lungs, a correct diagnosis of this condition has been made in nine instances during the last three years.

The patient was examined by roentgen rays on six occasions within two and a half years. These examinations showed an extremely slow advance of the primary intrathoracic lesion.

The intracranial exploration with the removal of tumor by Dr. Cushing two times in about thirty months is noteworthy. Indeed, but for the unfortunate accident of a pulmonary embolus, the patient's life would possibly have been prolonged for years, as in case 5.

CASE 7.—*Sudden onset of symptoms with twitching of muscles of face and aphasia. Cerebral tumor suspect. Cerebral exploration without result. Increase of symptoms; right hemiplegia. Reexploration with finding of tumor. Microscopic diagnosis: metastatic epithelial tumor. Death. No necropsy.*

History.—On June 25, 1925, James G., a native American, aged 56, was admitted for the second time, with a diagnosis of tumor of the brain. The patient was well until March 8, 1925; then he suddenly felt twitching of the muscles of the right side of the face with difficulty in forming words. Four days later he had three similar attacks. On March 26, 1925, a cerebral exploration was made, but a tumor was not located. After several deep roentgen treatments the patient was discharged. However, there was a rapid increase in his symptoms with paralysis of the right arm and leg and difficulty in speaking.

Physical Examination.—On this second admission, the patient was semiconscious. There was a right sided hemiplegia. The optic disks were swollen.

Course of Illness.—A preoperative diagnosis of glioma in the left parietal lobe was made, and at an exploration on June 27, 1925, Dr. Cushing removed the great part of a partly degenerated tumor. The lesion in the gross resembled a glioblastoma multiforme. Some time later, a diagnosis of malignant epithelial tumor, probably of pulmonary origin, was made. On July 21, 1925, a roentgen examination of the chest showed a large, rounded mass in the left upper lobe, and the diagnosis of primary tumor of the lung was made. The patient made an uneventful recovery and was discharged on July 28, 1925. He improved for a time and then became worse. He died at home on Oct. 26, 1925, about seven months after the onset of the cerebral symptoms. Necropsy was not made.

Microscopic Examination of Surgical Specimen.—The metastatic tumor was composed of cuboidal cells with large deep-staining, irregular nuclei. The cells were arranged in one or many layers to form glandlike structures. There was considerable necrosis. In the adjacent brain tissue was an evident gliosis with phagocytosis.

Comment.—The relief from symptoms in this case, as in case 2, was of a few months' duration only. We therefore believed that although palliative, a cerebral exploration was indicated.

CASE 8.—*Onset of illness with cough followed later by headache and loss of weight. Sudden onset of intracranial pressure. Roentgenologic demonstration of carcinoma of lung. Palliative suboccipital decompression with early fatality.*

History.—On Dec. 20, 1928, Owen O'D., a native American, aged 48, was referred to the medical service for observation. For one year before admission, the patient had a cough productive of thick, yellow sputum. Two months before the admission, he came to the outpatient service complaining of attacks of severe headache which had been present for about five months. The patient also stated that he had lost about 35 pounds (14 Kg.) in weight in the preceding year.

The patient was admitted to the hospital. A lumbar puncture was done on Dec. 1, 1928. The cerebrospinal fluid pressure and the results of various tests were within normal limits. He was discharged, but the increase in the severity of

his headaches and the onset of unsteadiness in gait and dimness of vision caused him to seek readmission to the medical service on Dec. 13, 1928. A gradual development of choked disks was found, and the patient was transferred to the surgical service on Dec. 20, 1928.

Physical Examination.—Despite the stated loss of weight, the patient was well nourished. Both optic disks showed about 3 diopters of swelling. Involvement of the right fifth, seventh and eighth cranial nerves was found. The gait was ataxic. There was no nystagmus.

Course of Illness.—A roentgen examination of the chest was difficult of interpretation and the diagnosis lay between tuberculosis of the left upper lobe and

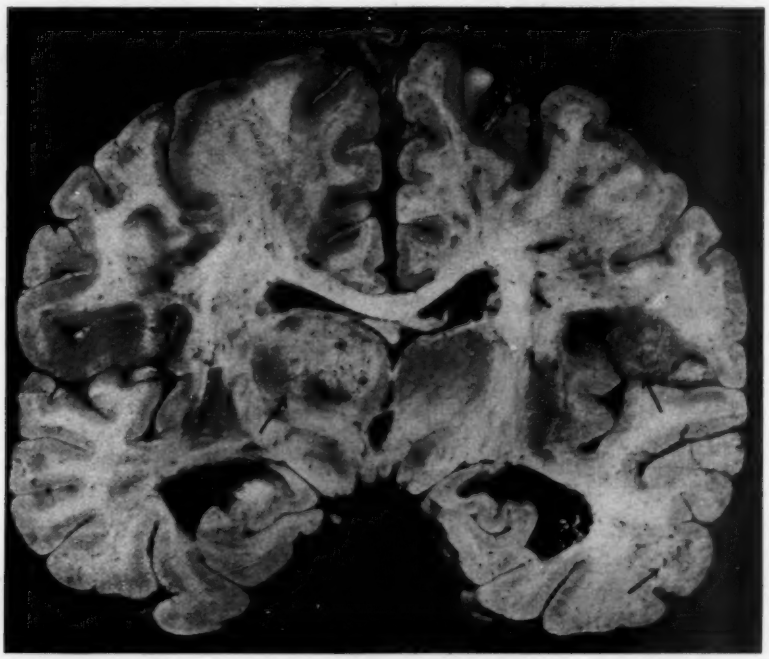

Fig. 11 (case 8).—Metastases in the cerebral hemispheres and in the basal ganglion (indicated by arrows).

tumor. A second roentgen examination of the chest, eight days after the first one, unquestionably showed the shadow of a tumor in the hilum of the left lung.

In the hope of aiding the patient by getting rid of the pressure symptoms, Dr. Cushing made a suboccipital exploration on Jan. 2, 1929, and removed one of the degenerated metastatic nodules from the left hemisphere of the cerebellum. Death occurred on Jan. 6, 1929. Complete necropsy was made.

Necropsy.—Postmortem examination showed primary carcinoma of the bronchus of the upper lobe of the left lung with metastases to the adjacent lymph nodes, pancreas, right kidney and multiple metastases to the brain; also acute necrotizing bronchopneumonia.

Multiple metastases in the brain were located as follows: in the right frontal lobe, in the basal ganglions on the left side (fig. 11), in the gray matter of the parietal lobe, in both hemispheres of the cerebellum and in the vermis. All

these nodules were grayish-red and sharply marked off grossly and showed little necrosis. The meninges did not show gross abnormalities.

Microscopic Description.—Lungs: The tumor cells were low cuboidal cells with small, hyperchromatic nuclei and little cytoplasm. They resembled the basal cells of the bronchial mucosa. The tumor invaded the walls of the blood vessel, and their lumina, as well as the lymphatics. They grew in nests in the alveoli and did not appear to line the walls of the alveoli. A great part of the remainder of the lungs was the seat of an acute inflammatory process.

Brain: The tumor appeared to be the most invasive of all of the metastatic pulmonary tumors. There were numerous polymorphonuclear leukocytes about and in the metastases, so that real microscopic abscesses resulted. Small nests of cells invaded blood vessel walls and lined the intima causing a thrombus formation in which blood and tumor elements were mixed. Similar nests of cells invaded the brain and leptomeninges. A tremendous number of phagocytes and a fibrillary astrocyte response, as well as changes in the microglia and acute swelling of the oligodendroglia were seen.

Comment.—Although the presence of a pulmonary tumor in this case was disclosed before the cerebral exploration was performed, decompression was decided on to alleviate the patient's suffering. The rapid fatal issue was due to a necrotizing pneumonia and also to the fact that the brain was heavily invaded by the malignant tumor.

CASE 9.—*Sudden onset with aphasia and right spastic hemiplegia. Early pressure symptoms. Cerebral tumor on left side suspected. Osteoplastic exploration with negative results. Death three weeks after operation. Necropsy.*

History.—On Dec. 31, 1928, Carrie S., an American housewife, aged 58, was referred by Dr. Fred M. Lowe of West Newton, Mass., with a diagnosis of tumor of the brain. The illness began suddenly on Oct. 5, 1928, about three months before admission while the patient was working at home. She felt her right arm and leg become weak and numb and noticed also dimness of vision. Her husband was soon aware of his wife's inability to form words and speak intelligibly, although she was able to understand. She was hospitalized. The increasing swelling of the optic disks suggested that an intracranial tumor was present.

Physical Examination.—The patient was obese. Motor aphasia, anosmia, right hemiparesis and hemiparesthesia were present. There was a high degree of swelling of the optic disks measured at 5 diopters. The extra-ocular movements of the left eye were present.

Course of Illness.—Because of the high grade of choked disk, a left osteoplastic exploration was made shortly after admission with the expectation of finding a glioblastoma multiforme. A tumor was not located, but the great edema of the brain forced the sacrifice of the bone flap. There was only a temporary improvement, and death occurred on Jan. 25, 1929, about three and one-half months from the onset of the symptoms. Complete necropsy was permitted.

Necropsy.—Postmortem examination revealed primary carcinoma of the middle branch of the right bronchus with metastases to the peribronchial lymph nodes, left lung, brain, liver, left kidney and left suprarenal gland.

The body was well nourished.

The carcinoma took origin in the bronchial mucosa. The greater part of the middle lobe was replaced by partly broken down new growth which on being sectioned resembled closely a blood vessel tumor. In addition, the artery to the

right lower lobe was completely occluded by a recent thrombus. The right common carotid artery was also occluded by a recent thrombus situated at a point where sclerotic changes of the vessel wall were most marked. The left lung contained one metastatic nodule.

In the brain, the entire left hemisphere was edematous. Just posterior to the site of operation in the parietal lobe there was a single metastatic nodule 3.5 cm. in diameter, which extended from just beneath the cortex. Many sections of the brain failed to show any further metastases.

Microscopic Examination.—Lungs: Necrosis and hemorrhage in the new growth were present to such an extent that there was little well preserved tumor. An inflammatory reaction of the walls of the large blood vessels, resulting in thrombosis, was a common observation, and this may account for the extensive necrosis.

The tumor cells were columnar, and were arranged as alveoli with papillary projections into the lumen.

Brain: The tumor cells in the one metastatic nodule were actively invading the adjacent brain from the meninges and from the periphery of the metastasis. More necrosis was seen about this single large metastasis than in any other material studied. There were multiple small collections of necrotic material and polymorphonuclear leukocytes resembling abscesses both at the periphery and among the tumor cells. In the paraffin sections were seen tremendous numbers of phagocytic cells in the adjacent brain. Frozen sections of the same material stained for microglia showed a most remarkable response on the part of these cells, demonstrating changes of these cells into actively phagocytic cells.

There was more clasmatodendrosis of the responding fibrillary astrocytes than was seen in other cases of this series. The oligodendroglia cells from all over the brain showed swelling of the cytoplasm.

The tumor cells were arranged as alveoli and were usually high columnar. However, many groups of cells were piled up to resemble transitional epithelium.

Comment.—The sudden onset with hemiplegia and aphasia suggested, at first, a cerebral vascular accident. With the finding of choked disks and increasing intracranial pressure, a diagnosis of cerebral tumor was made. The short history and the changes suggested the presence of the most invasive and rapidly growing of the gliomas, the glioblastoma multiforme. A tumor was not disclosed at operation, although the edema of the brain was such that the tissue was almost fluid.

The finding at necropsy of a primary carcinoma of the bronchus to the right middle lobe was unexpected. When the brain was sectioned, the tremendous edema and the single, localized and apparently enucleable metastatic nodule were found just posterior to the exploratory cerebral incision.

Roentgen examinations of the lungs were not made nor was an examination of the cerebrospinal fluid made during the course of the illness.

CASE 10.—*Occipital headaches followed by right hemiplegia and severe mental symptoms. Development of choked disks. Cerebral tumor of the left side sus-*

pected. Operation with finding of tumor in left motor area. Death. Necropsy. Finding of primary carcinoma of bronchus.

History.—On Nov. 25, 1927, Serafin G., a Spanish seaman, aged 67, was referred by the Boston Psychopathic Hospital with the diagnosis of tumor of the brain. The illness began two months before admission with weakness of the right leg and severe occipital headaches. Two weeks later, spastic paralysis of the right leg and then of the right arm developed. There was no history of symptoms of increased intracranial pressure. One month before admission, the patient was referred from a local hospital to the Psychopathic Hospital because of his mental symptoms. With the development of choking of both optic disks, he was referred to the surgical service of this clinic as suspected of having a cerebral tumor.

Physical Examination.—The patient was uncooperative, aphasic and difficult to examine. Both optic disks were swollen to about 3 diopters. A spastic paralysis of the right arm and leg with a positive sign of Babinski and ankle clonus were present. The results of the various laboratory tests were reported as normal. The roentgen examination of the skull showed no localizing signs of a tumor.

Course of Illness.—The preoperative diagnosis was difficult to arrive at. However, in view of the age and the short history of symptoms, a glioblastoma multiforme of the left motor area was considered as the most possible lesion. A left bone flap was made, and a nodule of tumor was easily enucleated from the motor area. An immediate examination suggested a metastatic adenocarcinoma. Portable roentgen ray films were made and interpreted as showing a large, rounded, soft tissue shadow in the outer portion of the right hilum. As the left side of the diaphragm was held high, it was thought that a primary tumor of the stomach was present with metastases to the lung and cerebrum. Evidence of an extensive respiratory infection began after the operation, and the patient died on Dec. 8, 1927, about two and a half months from the onset of the symptoms. Complete necropsy was made.

Necropsy.—Postmortem examination revealed a primary carcinoma of the bronchus of the right lung with multiple metastases to the brain, liver, suprarenal glands and right kidney, and extensive bronchopneumonia.

The body was well nourished.

The primary tumor involved the lower part of the upper lobe, the entire middle lobe and the upper part of the lower lobe of the right lung. The middle and lower bronchi were patent, but the upper bronchus was completely occluded, 1.5 cm. from its origin, by the carcinoma. The sections of the lung showed a solid grayish-white tumor invading the adjacent lung tissue.

Brain: Five large metastatic nodules were found in the left cerebral hemisphere, in the cerebellum and in the pons (figs. 12 and 13). One nodule in the cerebellum so compressed the fourth ventricle that the ventricular system was dilated. The nodules were grayish-red with little necrosis. They were round, appeared to be perfectly demarcated and indeed could be readily chucked out of the brain (fig. 12). The edema of the left hemisphere was remarkable in comparison with the relatively normal right hemisphere, in which no nodules were found.

Microscopic Examination.—Lungs: The sections through the primary tumor showed the invasive, rapidly growing, well preserved epithelial cells arranged, according to location, as glandlike structures or in small clumps. The entire wall of the primary bronchus was invaded, and the lining epithelium was replaced by tumor. Elsewhere in the lungs were edema, infarction and evidence of an acute

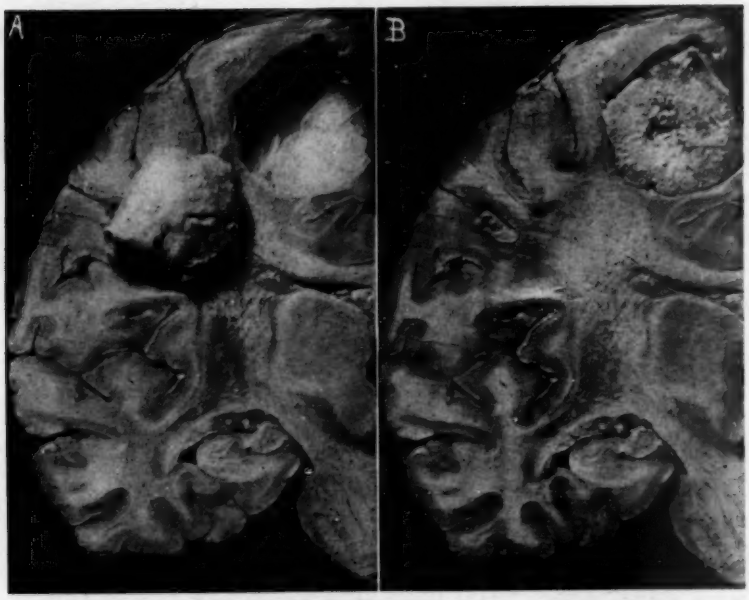

Fig. 12 (case 10).—An enucleable solitary metastatic nodule in the cerebrum (*A*) removed from its bed and (*B*) in place.

Fig. 13 (case 10).—Metastases in the cerebellum from a bronchiogenic carcinoma.

inflammatory process. Separate from the tumor and in an area of normal lung tissue was an early stage of metaplasia of the lining epithelium of a bronchiole.

Many small blood vessels and lymph vessels were filled with tumor emboli. The walls of some vessels were invaded by individual tumor cells.

Brain: There were available for study the immediately fixed operative specimen and the necropsy material, fixed six hours post mortem.

The cells of the metastasis were similar in arrangement and type to those of the primary tumor. The cytoplasm was plentiful, and the cells were either

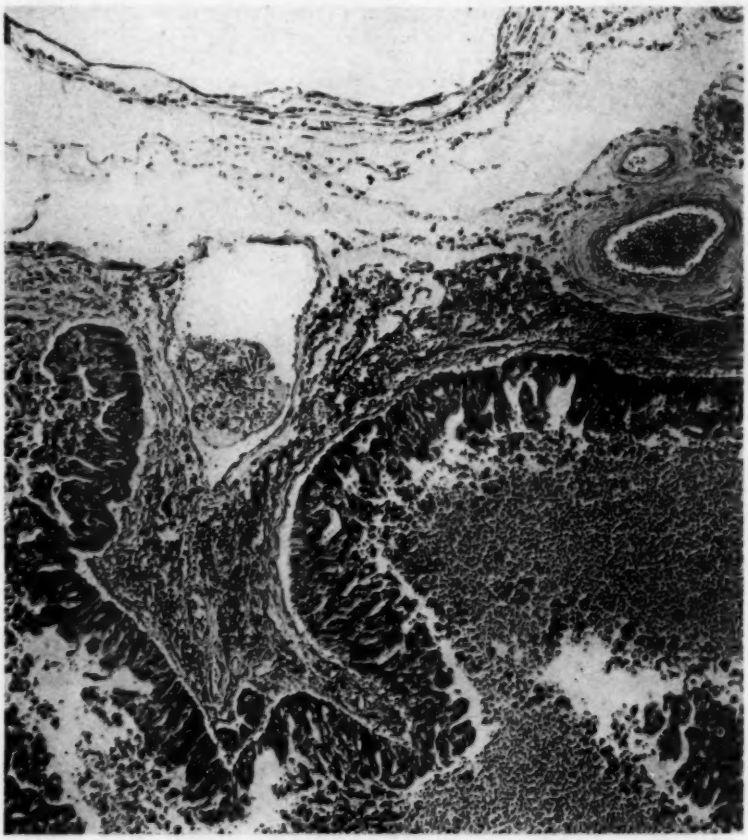

Fig. 14.—A section through the tumor nodule shown in figure 12. The cortex is completely replaced by tumor cells, which line the under surface of the pia mater. There is no invasion of the subarachnoid space. Hematoxylin and eosin; × 80.

columnar or high cuboidal and often occurred in many layers like the arrangement of transitional epithelium. Mitoses were abundant. The tumor invaded the brain along the periphery of small blood vessels, and by direct invasion of the tissue with groups of tumor cells (fig. 14). With the routine paraffin sections stained with eosin-methylene blue and phosphotungstic acid one could study many aspects of the injury to the brain and the brain's response.

For a short distance about the tumor, the brain tissue was necrotic, the nerve cells were disintegrated and the myelin sheaths were broken up, and one saw only the large phagocytic cells and the cell bodies and processes of both degenerated and active fibrous astrocytes. There was also seen a proliferation of the fibrous astrocytes for some distance away. Except for the phagocytosis and response of the astrocytes, no other part of an inflammatory response was to be seen.

The frozen sections stained specifically for astrocytes and for oligodendroglia and microglia demonstrated special changes in these elements. There were hyperplasia and hypertrophy of many of the fibrous astrocytes which "streamed" toward the metastasis (fig. 15). The degenerative change of these cells, clasmatodendrosis, was especially well shown.

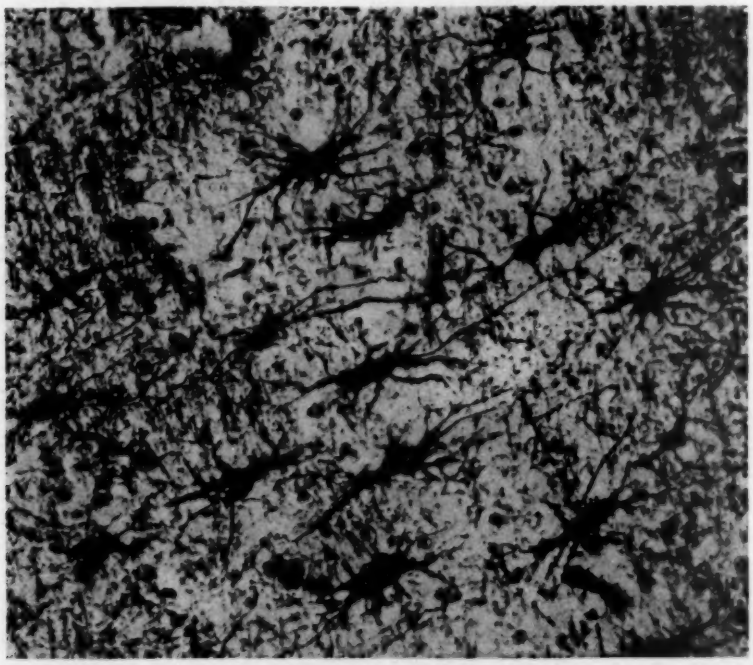

Fig. 15.—The reaction of fibrillary astrocytes in the vicinity of a cerebral metastasis from a primary cancer of the lung. There are a proliferation and an increase in size of these cells. The arrangement of these cells gives the impression that they are streaming toward the lesion. Gold chloride sublimate (Globus modification); × 320.

The oligodendroglia both in the specimen obtained at operation and in those obtained at necropsy were in the swollen stage, but there was no evidence of any activity on their part in the repair of the injury.

Just as Hortega and Penfield demonstrated the transformation of microglia into phagocytic cells about experimental wounds and tumors of the brain so one could follow these changes in the brain tissue about the metastases. A short distance from the edge of the tumor tissue, the microglia increased in numbers and soon changed their form to that of the type of phagocytic cell known as gitterzellen.

Comment.—The outstanding symptoms in this case were those of mental changes, leading to hospitalization in three separate hospitals before the changes in the eyegrounds suggesting an intracranial tumor were recognized at the Psychopathic Hospital. The aphasia and inability to obtain a concise history were the great stumbling blocks in the interpretation of the lesions. The choking of the disks occurred early after the onset of symptoms.

It is interesting to note that in the presence of a relatively small primary tumor there was an extensive invasion of the blood vessels by neoplastic cells and also multiple nodules in the brain.

In this case, as in cases 1 and 3, the roentgenologic examination of the lungs gave a negative result.

CASE 11.—*Onset insidious with tiredness, headache, nausea and vomiting. Subtemporal decompression. Glioma of right frontal lobe suspect. Osteoplastic exploration on right side with removal of tumor. Early fatality. Necropsy with finding of primary carcinoma of the lungs and multiple metastases to brain.*

History.—On Dec. 15, 1913, Miss A. W., an American nurse, aged 48, was referred by Dr. J. T. Mitchell of Middleton, Conn., with a diagnosis of tumor of the brain. Previous to the onset of the illness, the patient had been treated for asthma for several years. The exact onset of the present illness was difficult to determine. The patient felt tired in February, 1913, but continued at work. Seven months later, in September, 1913, she had the first of a series of frontal and suboccipital headaches accompanied by nausea and vomiting. Various treatments were outlined and given, but with no relief. Finally, a diagnosis of cerebral tumor was made.

Physical Examination.—The patient was well developed and well nourished. There was a high degree of choking of the optic disks. The tongue protruded to the right. Aphasia was noted. Ataxia of the extremities and exaggeration of the deep reflexes were conspicuous.

Course of Illness.—A definite localization of the tumor could not be made. A subtemporal decompression was made on Dec. 21, 1913. In the next several weeks, the patient became worse, and finally epileptiform attacks suggested a cerebral lesion on the right side, and an osteoplastic exploration was made by Dr. Cushing on Jan. 13, 1914. An unusually edematous brain was found and a "gelatinous," stringy, mucoid tumor about 3 cm. in diameter was removed from the right frontal lobe. There was an early postoperative fatality.

Necropsy.—The body was well nourished. A primary carcinoma of the bronchus to the right lower lobe with metastases to the brain was present.

Brain: The brain was edematous and protruded through the operative defect in the skull. There were innumerable small and large cystic cavities measuring from 0.5 to 3 cm. in diameter and filled with a gelatinous, stringy material. These were found everywhere in the brain, being evenly distributed and suggesting an arterial spread.

Microscopic Examination.—A number of sections through the specimen removed at operation and of specimens taken from the brain at necropsy were studied. There was extensive necrosis in the center of each of the metastases and at the periphery, in the brain substance. The tumor cells were columnar and polygonal, with abundant mitoses, and were arranged to form small cysts or

glands. Tumor cells were found in the walls of blood vessels and in their lumen, as emboli and thrombi, and also as cuffs about the adventitia. The leptomeninges over the cerebrum were lined in one portion by tumor cells.

Comment.—This case belongs to the early series in which the patients came to the hospital for treatment. There was an early fatal issue, and the necropsy revealed a bronchiogenic tumor.

The finding of a primary carcinoma of the lungs was unexpected. In retrospect, the recommending physician recognized that the patient's heart was displaced and that the area of cardiac dulness was increased, suggesting some abnormality of the midthoracic region. The presence of the pulmonary tumor probably accounts for these physical abnormalities. The insidious onset of the cerebral symptoms was more in keeping with a primary tumor of the brain than with a metastatic lesion. As is often the case with metastatic lesions to the brain, the clinical picture was a confusing one and the localization most difficult.

The multiple metastases suggested an arterial spread of the neoplasm.

CASE 12.—*Onset sudden with paralysis of the left side of the face. Disorientation. Dysarthria. Early choking of optic disks. Regarded as alcoholic psychosis. Death without operation. Necropsy with finding of carcinoma of bronchus and multiple metastases to various organs, brain and leptomeninges.*

History.—On Oct. 23, 1921, George S., an English chef, aged 55, was admitted to the surgical service for observation. The onset of the illness occurred suddenly on Sept. 20, 1921, with a paralysis of the left side of the face. In addition, the patient was temporarily disoriented. Following the onset dysarthria, mental changes and the symptoms of increased intracranial pressure developed.

Physical Examination.—The patient was disoriented, restless and emaciated. A left facial paralysis was noted. There was a slight choking of the optic disks. The results of the examinations of the blood, urine and spinal fluid were negative. The blood pressure was elevated, with a systolic pressure of 160 mm. and a diastolic pressure of 80 mm.

Course of Illness.—A diagnosis of alcoholic psychosis was made, as it was known that the patient was a heavy user of alcohol. Signs of consolidation of the left lung were evident shortly after admission, and death occurred sixteen days later.

Necropsy.—Postmortem examination showed a primary carcinoma of the bronchus to the lower lobe of the lung with metastases to the brain, suprarenal glands, liver, hilar lymph nodes, right lung and upper lobe of the left lung.

The body was well nourished. The left pleural cavity contained about 30 cc. of blood-tinged fluid. A firm, grayish-white tumor, about 7 cm. in diameter, surrounded and invaded the bronchus to the lower lobe of the left lung. The tumor projected into the lumen of this bronchus so as almost completely to occlude it. The tumor extended in fine strands from its periphery into the adjacent pulmonary tissue. There were innumerable small, nodular metastases, never larger than 0.5 cm. in diameter, scattered throughout the rest of the tissue, but especially beneath the visceral pleura.

Brain: Multiple metastases were found in the brain, in the leptomeninges of the brain and spinal cord and along the dorsal root ganglions.

The largest nodule in the brain was located in the left occipital lobe. It measured 5 by 3 cm. Other smaller nodules were found along the sylvian fissure, in the floor of the fourth ventricle, in the caudate nuclei and in innumerable other areas. All these nodules were grayish pink and appeared to be sharply marked off from the surrounding tissue.

Local thickening of grayish-white metastatic nodules was seen in the leptomeninges in the cervical and thoracic region, about all the dorsal root ganglions.

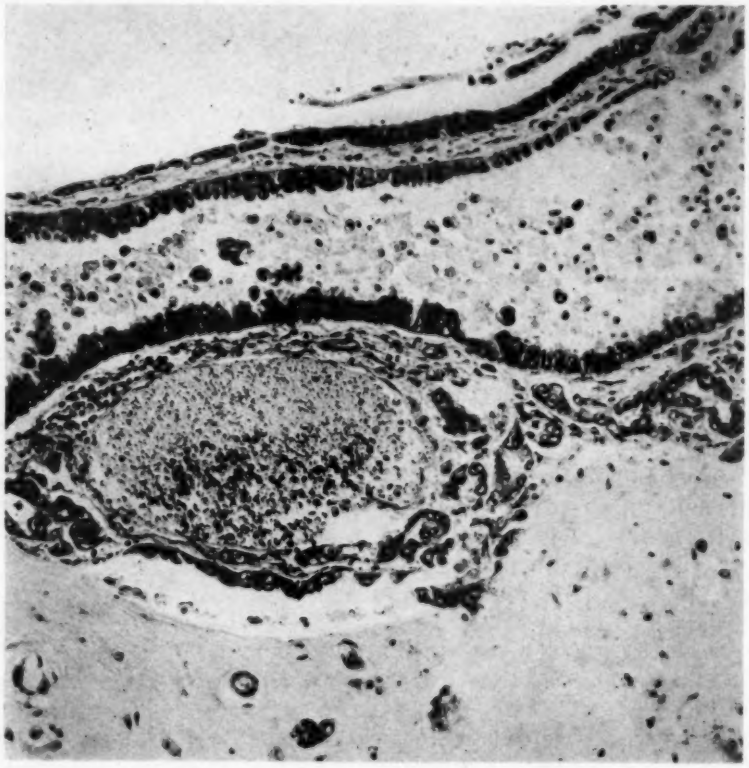

Fig. 16.—The leptomeninges are lined by neoplastic cells from a primary carcinoma of the lungs (localized meningitis carcinomatosa). Tumor cells are seen in the subarachnoid space and in the cerebral cortex. Eosin-methylene blue; × 150.

Microscopic Examination.—Lungs: There was much necrosis of the tumor. A great number of blood and lymph vessels had their walls infiltrated and their lumen partially or completely occluded by tumor cells. Throughout the lungs were multiple scattered metastases, which appeared to have been transported by the blood stream.

Brain and Meninges: Both sharply demarcated and infiltrating tumor masses involved the brain, the leptomeninges of the brain and of the spinal cord and even some of the spinal nerves. The cells grew along the surface of the leptomeninges and replaced the usual lining (fig. 16).

It is of interest that while ordinarily the tumor cells were columnar, when they lined the subarachnoid spaces and extended out into the dorsal root ganglions they took on a cuboidal aspect. No invasion of the spinal cord was seen.

Comment.—The sudden onset of cerebral symptoms with mental changes in this patient, who was an addict to alcohol, suggested an alcoholic psychosis to the examiners. The absence of complaints and of any history referable to the respiratory tract in the presence of such an advanced lesion in the lungs is noteworthy. In the central nervous system, the tumor invaded the cerebral substance, the leptomeninges of the hemispheres and likewise those of the cord, which is unique.

CASE 13.—*Onset of illness with pain in lumbar region and inability to walk. Exploratory laparotomy with finding of myomas of uterus. Postoperative wound infection and consolidation of base of left lung. Death. Necropsy with finding of primary carcinoma of bronchus to left lower lobe with metastases to brain, pelvic bones, liver, suprarenal glands, brain and to a meningioma of brain.*

History.—On March 13, 1923, Minnie C., a Jewish housewife, aged 57, was referred by Dr. C. E. Williams of Roxbury, Mass., for observation. The illness began five months before admission with a dull pain in the lower part of the back and inability to walk. About two months later, the first of a series of persistent night sweats began. Within a short time before admission, the patient expectorated a small amount of blood.

Physical Examination.—The patient was well nourished. There was rigidity in the lower part of the abdomen with tenderness in the left lower quadrant. Several nodules were felt in the left side of the body of the uterus. The examination of the thorax and lungs showed no abnormality. A neurologic examination likewise showed no disease. The cerebrospinal fluid was normal. The roentgen examination of the chest showed a wedge-shaped area of consolidation in the left lower lobe, the nature of which was not explained.

Course of Illness.—After a thorough study, no lesions were demonstrated in the genito-urinary, gastro-intestinal, biliary or nervous systems. A pelvic exploration was made, and a hysterectomy was performed because of the myomas. The operative wound became infected, and the patient showed all the symptoms of increasing involvement of the lower lobe of the left lung. Death occurred two and a half months after admission to the hospital. A complete postmortem examination was made.

Necropsy.—Postmortem examination showed a primary carcinoma of the bronchus to the lower lobe of the left lung with metastases to the lung, pelvic bones, liver, suprarenal glands, brain and the meningioma.

Lungs: A short distance from its origin, the bronchus to the lower lobe of the left lung was partially occluded by a carcinoma which extended from this bronchus for about 3 cm. into the lung tissue in all directions. The mucosa of this bronchus was eroded as the tumor projected into the lumen and for some distance to each side. The peribronchial lymph nodes were replaced by tumor.

Brain: The convolutions were flattened. One metastatic nodule, 1.5 cm. in diameter, was found in the left posterior parietal region. A meningioma, 2 cm. in diameter, was found over the right frontal lobe. This tumor caused erosion of the overlying cranium. A section of this hard tumor revealed areas of grayish-white tissue mixed with the dense, calcareous meningioma.

Microscopic Examination.—Lungs: The cells of the primary tumor were cylindric and were arranged as alveolar structures. The walls of blood vessels and their lumina contained nests and clumps of tumor cells.

Brain: The section through the metastatic nodule showed it to be of the same structure and cell type as the primary tumor. The invasion of the meningioma represented a most unusual and rare instance of a benign new growth being invaded by a malignant tumor.

Comment.—This case belonged to the "old" series of cases in which the patients came to this hospital before a study of this condition was inaugurated by one of us and attention called to the frequent occurrence of this disease. Although the patient gave a history of hemoptysis and of night sweats, and although roentgen examinations pointed toward pathologic changes in the chest, no particular attention was paid to the thoracic organs. The patient then went through a pelvic operation, remaining in the hospital seventy-five days without the bronchiogenic tumor being recognized.

This patient also is of interest in that in addition to the bronchiogenic cancer she had a myoma of the uterus and a meningioma. The latter was infiltrated by the pulmonary cancer, which also had metastasized to the brain.[18]

CASE 14.—*Sudden onset of cerebral symptoms with headache. Hemiplegia on the left. Cough for five years. Early fatality. Necropsy with finding of primary carcinoma of bronchus and metastases to the brain.*

History.—K. L., a man, aged 45, was admitted to the Cambridge (Mass.) Hospital with the complaint of severe headache and pain in the back and neck. For five years before admission, the patient had had a cough. The onset of cerebral symptoms was sudden eight days before admission, with a severe, generalized and continuous headache.

Physical Examination.—The patient was emaciated. There were signs of an active abnormal process over the apex of the left lung.

Course of Illness.—There was a gradual development of a left hemiplegia, and the patient died seven days after admission and about fifteen days after the onset of the cerebral symptoms. A complete necropsy was performed.

Necropsy.—Primary carcinoma of the bronchus to the upper lobe of the left lung was found, with metastases to the adjacent lymph nodes and brain.

Lungs: The upper central division of the primary bronchus to the upper lobe of the left lung was the apparent seat of the primary carcinoma that invaded almost the entire upper lobe. The tumor apparently advanced eccentrically and uniformly from this one point of origin. The lymph nodes at the bifurcation of the trachea were massive from metastases.

Brain: The meninges and blood vessels appeared normal grossly. After the brain was sectioned, five separate well preserved metastatic nodules, measuring from 1 to 4 cm in diameter, were found in the right frontal, parietal and occipital lobes and in the right cerebellar hemisphere.

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18. Fried, B. M.: Metastatic Inoculation of a Meningioma by Cancer Cells from a Bronchiogenic Carcinoma, Am. J. Path., to be published.

Microscopic Examination.—The primary tumor was made up of columnar cells. arranged in alveolar form. The cells were not ciliated nor did they produce mucus. They appeared to grow along the walls of the alveoli. Many blood vessels were invaded and occluded by tumor.

The cells of the metastases to the brain were similar to those of the primary tumor. There was considerable necrosis of the tumor and also an extensive necrosis of the brain about the metastasis.

Comment.—It is likely that the tumor of the left lung was of long standing, as the patient had a chronic cough for five years. The symptoms of metastases to the brain were of short duration, and the condition and extent of these metastases suggested that they were of recent origin and had occurred at about the same time. It is also of interest that all the metastases were on the right side of the brain, as in all the cases studied, the primary tumor had invaded the walls and lumen of many of the pulmonary vessels.

CASE 15.—*Onset with pain in right shoulder, weakness and loss of weight. Cough. Pulmonary tuberculosis suspected. Rapid course to fatality. Necropsy.*

History.—A man, aged 37, entered the Boston Sanatorium with the complaint of pain in the right shoulder and right knee. About three months before admission, the patient had had a sharp pain in the right shoulder, not related to injury. Soon diarrhea, weakness, loss of weight, an evening rise of temperature to 100 F. and signs of involvement of the right lung caused the patient's hospitalization. There was a short history of cough with but little expectoration.

Physical Examination.—The patient was emaciated. The chest was asymmetrical with a diminution of expansion on the right side. There were dulness and bronchial breathing over the entire right side of the chest and apical region of the left lung. The bones showed a chronic hypertrophic osteo-arthropathy. The temperature increased to 100 F. in the evening.

Course of Illness.—During a three months' stay at the hospital the patient had severe pain along the spine, and during the last week he was delirious. Death occurred six months from the onset of the symptoms. The final diagnosis was that of chronic and acute pulmonary tuberculosis and chronic hypertrophic osteo-arthropathy.

Necropsy.—Postmortem examination disclosed primary carcinoma of the bronchus to the upper lobe of the right lung with metastases to adjacent lymph nodes, left lung, left kidney, brain and right femur and chronic hypertrophic osteo-arthropathy.

Brain: Twelve large, softened metastases from 1 to 1.5 cm. in diameter were found scattered in every part of the brain.

Microscopic Examination.—The primary tumor replaced the pulmonary tissue, and in places the columnar cells growing in alveolar manner were replaced by squamous-like cells. Frequently, the walls of the blood vessels were invaded by the tumor cells, and the lumina occluded by a carcinomatous endophlebitis with resultant thrombus formation by both tumor and blood elements.

The metastases to the brain caused abundant necrosis and little reaction, as seen by the hematoxylin and eosin stained sections. The brain was invaded by tumor cells singly and in groups following along the blood vessels adjacent to the metastasis.

Summary of Cases

Case	Sex*	Age	Pulmonary Symptoms	Onset of Cerebral Symptoms	Optic Disks	Clinical Diagnosis	Cerebral Exploration and Result	Pathologic Diagnosis	Survival Following Operation
1	♂	67	None	Sudden with tingling of left arm and numbness	Showed no choking	Tumor of the brain	Removal of nodule from right postcentral convolution	Carcinoma metastatic from lung	Two years and four months
2	♂	44	None	Gradual with general weakness and pains throughout body	Showed advanced choking	Tumor of the brain	Removal of tumor from right precentral area	Bronchiogenic carcinoma metastatic to brain	(Postoperative fatality)
3	♂	49	None	Sudden with headaches, unconsciousness and convulsions	Choked	Tumor of the brain	Removal of tumor nodule	Bronchiogenic carcinoma widespread metastases	Seven months
4	♂	41	Nonproductive cough	Sudden with weakness in right foot and choked hemiplegia	Choked	Tumor of the brain	Removal of cystic mucoid tumor	Carcinoma metastatic from lung	Seven months
5	♂	70	None	Gradual development of paralysis of right arm and leg; apraxia	Choked	Tumor of the brain	Removal of tumor from left motor area	Carcinoma metastatic from lung	Seven years (!)
6	♀	46	None	Sudden with severe headaches	Choked	Tumor of the brain	Removal of tumor and of a large cyst	Carcinoma metastatic from lung	Two years and six months
7	♂	56	None	Sudden with twitching of facial muscles and paraphasia	Choked	Tumor of the brain	Removal of tumor	Carcinoma metastatic from lung	Five months
8	♂	48	Productive cough of one year's duration	Gradual with attacks of headache	Choked	Metastatic tumor of brain	Removal of metastatic tumor	Bronchiogenic carcinoma metastatic to brain	(Postoperative fatality)
9	♀	58	None	Sudden with numbness of right arm and dimness of vision	Showed advanced choking	Tumor of the brain	Tumor not found	Bronchiogenic carcinoma; widespread metastases	(Postoperative fatality)
10	♂	67	None	Gradual with occipital headaches and hemiplegia	Choked	Tumor of the brain	Removal of tumor nodule	Bronchiogenic carcinoma; widespread metastases	(Postoperative fatality)
11	♀	48	Asthma for several years	Gradual with frontal and suboccipital headaches	Showed advanced choking	Tumor of the brain	Removal of gelatinous tumor	Bronchiogenic carcinoma; multiple cerebral metastases	(Postoperative fatality)
12	♂	56	None	Sudden with left facial paralysis and disorientation	Showed slight choking	Alcoholic psychosis	Brain not explored	Bronchiogenic carcinoma; widespread metastases	(Death without operation)
13	♀	57	Hemoptysis on one occasion; night sweats	No cerebral symptoms	Not examined	Leiomyoma of uterus	Brain not explored	Bronchiogenic carcinoma; widespread metasteses to viscera, bones and brain	(Death without operation)
14	♂	45	Cough of five years' duration	Sudden with severe headaches	Not examined	Pulmonary tuberculosis	Brain not explored	Bronchiogenic carcinoma with metastases	(Death without operation)
15	♂	37	Cough	Sudden with delirium	Not examined	Pulmonary tuberculosis	Brain not explored	Bronchiogenic carcinoma; widespread metastases	(Death without operation)

* In this table, ♂ indicates male; ♀, female.

Comment.—The bronchiogenic cancer in this case metastasized to the viscera, the bones and the brain. The history is lacking in details concerning the symptomatology and the duration of the cerebral involvement.

GENERAL COMMENT

Pathologic Observations.—Lungs: In eleven cases, the primary tumor was located near the hilum of the lung and originated in a primary bronchus or in one of its early divisions. The tumor led to a thickening of the bronchial wall for a short distance and extended out into the adjacent pulmonary tissue, replacing it either diffusely or by fine projections. The lesion did not reveal a spread to the visceral pleura except in the instances in which the hilar portion of the right middle lobe was involved, and then the tumor extended into the adjacent portions of the upper and lower lobes.

The new growth presented a translucent surface studded with pigment and opaque, necrotic tissue. One tumor of the middle lobe of the right lung along with the pulmonary tissue became so necrotic and infiltrated with blood that it resembled more a primary "blood vessel" tumor than a malignant epithelial neoplasm.

In most sections through these tumors there were seen small and large blood vessels occluded by recent or organized thrombi, and in one instance the tumor extended into a large vessel adjacent to the primary bronchus involved. Frequently, small infarcts of the lungs were seen. Occasionally, small nodular metastases to the same or to the opposite lung were noted, and in one instance the metastases were distributed as are the tubercles in miliary tuberculosis.

The adjacent tracheobronchial lymph nodes showed a varying degree of invasion by metastases, but they were never greatly enlarged.

There were always changes in the lobe of the lung which was the site of the tumor, as well as elsewhere in the pulmonary tissue. Such changes as atelectasis and compensatory emphysema, infarction and acute inflammatory processes were commonly found adjacent to the tumor as elsewhere.

The microscopic examination of these bronchiogenic tumors emphasized the variations in the types, the arrangements and the invasiveness of the malignant cells. Although there was always a variation in the size of the cells, even in the same sections, one type predominated in both the primary tumor and the intracranial metastases. The cells of this common type were columnar or cylindric and were arranged in a single layer or piled up to line a variable-sized alveolar-like structure into which there were often papillary projections of the cells. In the same tumor, cuboidal or large polygonal cells were also seen, singly, in groups or arranged in a glandlike structure. In two of the tumors, cuboidal

cells predominated. Neither squamous cells nor the small, undifferentiated cells described as "oat cells" were seen, and in no instance were the cells considered as having their origin from the mucous glands of the bronchi or from the "alveolar epithelium."

The degree of invasiveness varied in that in some there appeared little reaction on the part of the bronchus or pulmonary tissue; while in others the tumor cells appeared isolated in a dense, old scar tissue. In all the cases there was erosion of the bronchial epithelium with extension into the lumen and invasion of the bronchus. The cartilage, blood vessels and lymphatics were involved as much as the parenchyma.

The lesions in the blood vessels were most interesting. Tumor cells invaded the walls of vessels, of any caliber, projected into the lumen and frequently formed a new lining for the vessel. A thrombus composed of tumor cells and of blood elements often formed and became organized and canalized, and the canaliculi themselves then became lined with tumor cells (figs. 3, 4, 5, 6 and 7).

Likewise, emboli made up of tumor cells were present in vessels of all calibers. Apparently, tumor emboli passed directly to the heart and from there into the general circulation, forming also metastases in distant visceral organs.

The atelectasis, hemorrhages, infarctions, emphysema and inflammatory processes seen in the gross were confirmed in all the microscopic sections.

Brain: Edema of the brain was noted at every intracranial operation and at necropsy. This was so conspicuous that the presence of the metastatic nodule never satisfied the operator that it alone could be the cause of such an edema, which often required the sacrifice of the bone flap.

Multiple thin coronal sections were made of each brain. The ventricles were never greatly dilated, and the choroid plexus always seemed normal in the gross. Likewise, the cerebrospinal fluid showed no pathologic changes.

The metastases were firm, solid, enucleable masses, measuring up to 5 cm. in diameter, large, enucleable, cystic masses as much as 9 cm. in diameter or necrotic, broken down lesions and as such resembled the most malignant and invasive of the gliomas, the glioblastoma multiforme. The solid metastases weighed as much as 50 Gm. The cystic metastases always had one or more mural nodules of typical carcinomatous tissue and had contents of more than 75 cc. of dirty, orange-colored mucoid material containing cholesterol crystals, phagocytic cells and débris. In one instance, bacteria were seen in smears of the cyst content, but culture of this material showed no growth.

In two cases there were single, apparently enucleable masses, 5 cm. in diameter. In three cases there were from six to twelve nodules of varying sizes located on the same side of the brain in each instance. Each of the remaining brains appeared to be literally riddled with about 100 separate masses, each of the same gross appearance. These appeared less enucleable and more invasive than the single metastases.

The location of the metastases is of interest in that in eight of eleven cases in which operation was performed, tumor was diagnosed and subsequently found in the motor areas. In two other instances, the lesion was correctly localized in the occipital region. In two patients, gross involvement of the leptomeninges of the cerebrum and spinal cord was seen in these thickened, grayish-white structures (fig. 16).

The diffuseness and multiplicity of the metastases to the brain were convincing evidence of their being carried by the blood stream.

From the material removed at operation and at necropsy, certain aspects of the reaction of the brain to the tumor, hitherto undescribed, could be studied.

In general, the cells resembled those of the primary lesion, except that they were more frequently in mitosis. However, when these cells invaded the tissue of the brain singly or in small groups, they differed from the common cell type of the pulmonary tumors, in that they often were huge and rounded or polygonal and had large, irregular, hyperchromatic nuclei. The cell arrangement was similar to that in the primary tumor except for certain features. In one instance, a single layer of tumor cells lined the subarachnoid space of both the brain and the spinal cord just as the tumor cells lined the alveoli of the lungs (fig. 16). Thick collars of tumor cells often surrounded the adventitia of blood vessels invading the brain alongside the vascular wall. The walls of large blood vessels at the periphery of some of the metastases were invaded by single cells or groups of tumor cells (figs. 6 and 7).

The nerve fibers showed complete destruction in the close vicinity of the metastatic nodules. In areas remote from the lesion, the nerve fibers showed demyelinization, swelling and fenestration. Changes in the ganglion cells were conspicuous in regressive and progressive changes in the cell body and in the nuclei, and also in the abnormal distribution of the Nissl substance.

In the paraffin sections, necrosis of the cerebral tissue and degeneration of the nerve cells and nerve fibers in the presence of some phagocytic cells and astrocytes was all that was visible of the reaction. But with the special stains referred to, the complexity of the reaction was conspicuous.

The activity that each individual cell displayed in the presence of the neoplastic invaders may be considered separately.

In general, the reaction in the brain closely resembled that described by Penfield [19] as present in the vicinity of gliomas and also in experimental cerebral injury.

The microglia appeared normal at a distance of 1 cm. from the edge of the metastasis. As the tumor nodule was approached, there was a rather abrupt transition to a mass of microglia which appeared to be wandering toward the necrotic tissue. Here the normal and also the transitional forms of this cell formed a dense black mass that thinned out as the actual necrotic zone was reached. Within a small area, all the changes from the normal microglia to the ameboid forms and the compound granular corpuscles were to be seen. The tumor masses themselves showed no penetration by the phagocytic and scavenger elements (figs. 17 and 18).

Large phagocytic cells were likewise seen attached to and lying free about the adventitia of small blood vessels at the boundary of the tumor and the necrotic cerebral tissue. It is possible that some of these cells arose from the adventitia of the blood vessels (the adventitial cells of Marchand).

Similarly, the astrocytes responded to the malignant neoplastic elements. In the cerebral tissue close to the metastasis, clasmatodendrosis of these cells was conspicuous (fig. 19). In the adjacent areas, a dense gliosis was present and then there was a stream of the astrocytes, all seeming to go in parallel rows toward the injury (fig. 15).

There was no evidence that the oligodendroglia act as an element of phagocytosis or of repair.[20] In every section of the material obtained at operation or at necropsy, varying degrees of swelling of the cells were conspicuous (fig. 20). It may be said that no distinction could be made between the swollen cells found in the old, fixed necropsy material and the fresh tissue operation obtained at and those seen in apparently normal brains. Transformation of these cells into phagocytic cells, as noted by some writers [20] in experimental conditions, could not be identified.

In brief, then, all elements of the cerebral substance responded to the metastatic neoplastic invasion. The reaction was most outstanding, and, as stated, closely resembled that seen by Penfield and his associates in experimental studies on the cerebral reactions to wounds and to infectious invaders.

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19. Penfield, W.: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77, 1925; The Mechanism of Cicatricial Contraction of the Brain, Brain **50**:429, 1927. Penfield, W., and Buckley, R. C.: Punctures of Brain: Factors Concerned in Gliosis and in Cicatricial Contraction, Arch. Neurol. & Psychiat. **20**:1 (July) 1928.

20. Ferrara, Armando, and Davidoff, L. M.: The Reaction of the Oligodendroglia to Injury of the Brain, Arch. Path. **6**:1030 (Dec.) 1928.

In his recent monograph, Lewin [21] stated that the brain represents an "indifferent nonspecific nutrient medium" for heterologous neoplasms. In 1923, Murphy and Sturm [22] found that transplantable mouse tumors grew actively when inoculated into the brains of rats, guinea-pigs and pigeons, whereas subcutaneous or intramuscular grafts in the same animals failed. It will be seen that in the material here presented the cerebral reaction toward metastases, which are in a sense a homologous

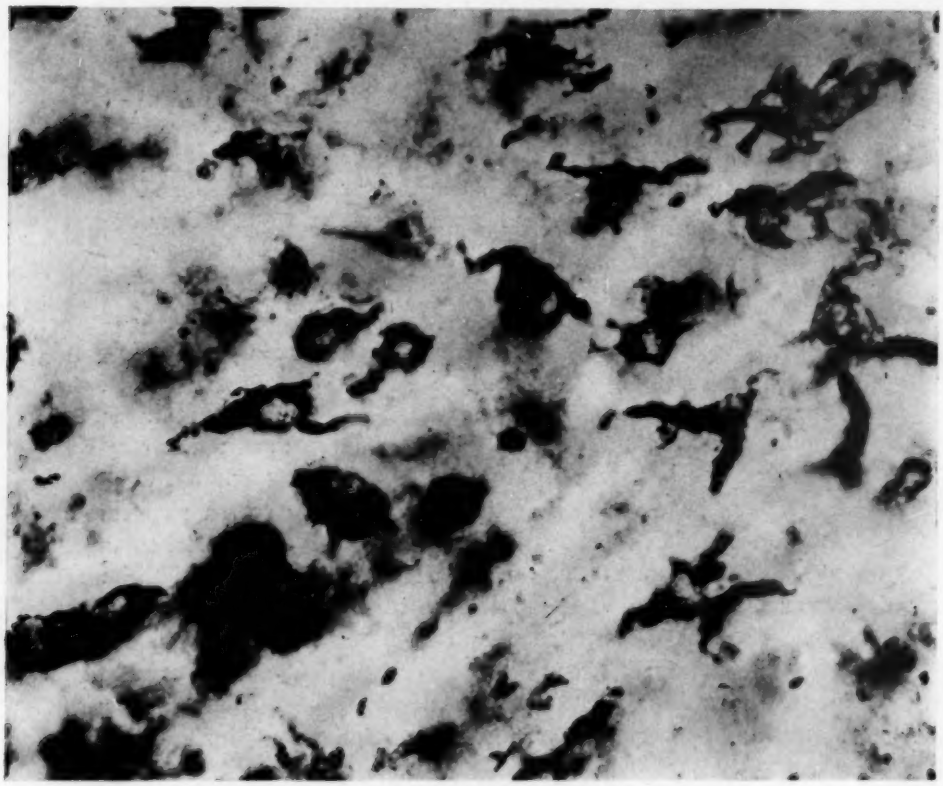

Fig. 17.—The reaction of the microglia to the metastases from a primary carcinoma of the lung. In the right segment of the picture the microglia show swollen processes. In the center, the processes are shortened and thickened, while in the left lower segment the cells are seen as compound granular corpuscles. Penfield's combined method for oligodendroglia and microglia; × 850.

graft, is of such a magnitude that one can hardly accept the notion that the cerebral substance is an "indifferent nonspecific medium." Never-

21. Lewin, Carl: Die Aetiologie der bösartigen Geschwülste, Berlin, Julius Springer, 1928.

22. Murphy, J. B., and Sturm, E.: Conditions Determining the Transplantability of Tissues in the Brain, J. Exper. Med. **38**:183, 1923.

theless, the malignant cells overcome this reaction and probably grow more rapidly in the brain than in the lungs.

Clinical Observations.—Onset of Symptoms: In nine of the fifteen cases, the disease started suddenly, and in six it began less abruptly. The patients of the first group could state accurately the circumstances, the date and often the hour of the onset of the first attack. In six of the nine patients, the initial symptoms were those of involvement of

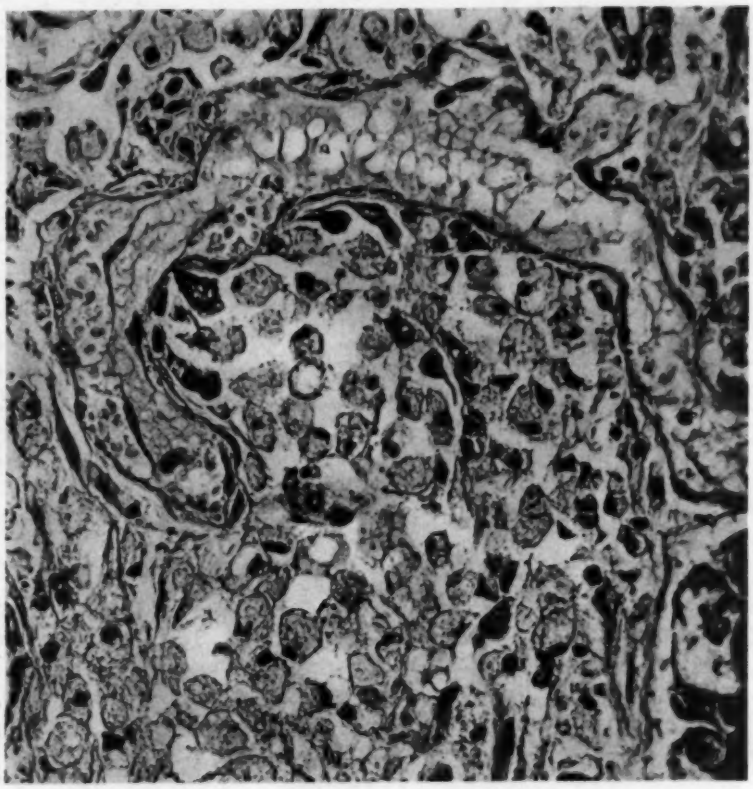

Fig. 18.—Macrophage reaction in the brain tissue adjacent to a metastatic nodule. Some of the macrophages lay close to or are attached to the wall of the blood vessel and give the impression that they originate and separate off from the adventitia. Hematoxylin and eosin; × 320.

a motor area of the brain resulting in jacksonian attacks, weakness or hemiplegia. Of the other three patients, two complained of headaches and one became delirious at the onset and died one week later.

In six cases of the second group, the onset, as stated, was less abrupt; in three of this group, the first symptoms were those of involvement of the motor areas, and in two the illness began with headaches. In one patient, the symptoms were most indefinite, and although an

intracranial lesion was suspected it could not be localized. Briefly stated, nine of the patients had as their initial symptom weakness of one extremity, convulsive seizure or hemiplegia, and four complained of headaches first.

Physical Examination: The patients were not emaciated, nor did they show a marked loss of weight.

No noteworthy abnormal observation was recorded in the examination of the thoracic organs, except in the case of two patients seen in

Fig. 19.—Clasmatodendrosis in the vicinity of a metastasis to the brain from a primary carcinoma of the lung. Gold chloride sublimate (Globus modification); × 850.

other hospitals in whom the physical signs were those of a lesion in the lungs compatible with pulmonary tuberculosis.

The optic disks in thirteen cases were examined, and a bilateral papilledema was found in twelve. In some of these cases there was evidence in the new formation of tissue that the choked optic disks had been present for some time. These observations are not in accord with those recorded in the literature that choking of the optic disks is

uncommon or that it occurs late in the course of the illness from a metastatic lesion to the brain.

From the results of the neurologic examination, a cerebral lesion was correctly localized in eight of eleven cases, and this was confirmed in each instance by an intracranial operation. In each of these eight

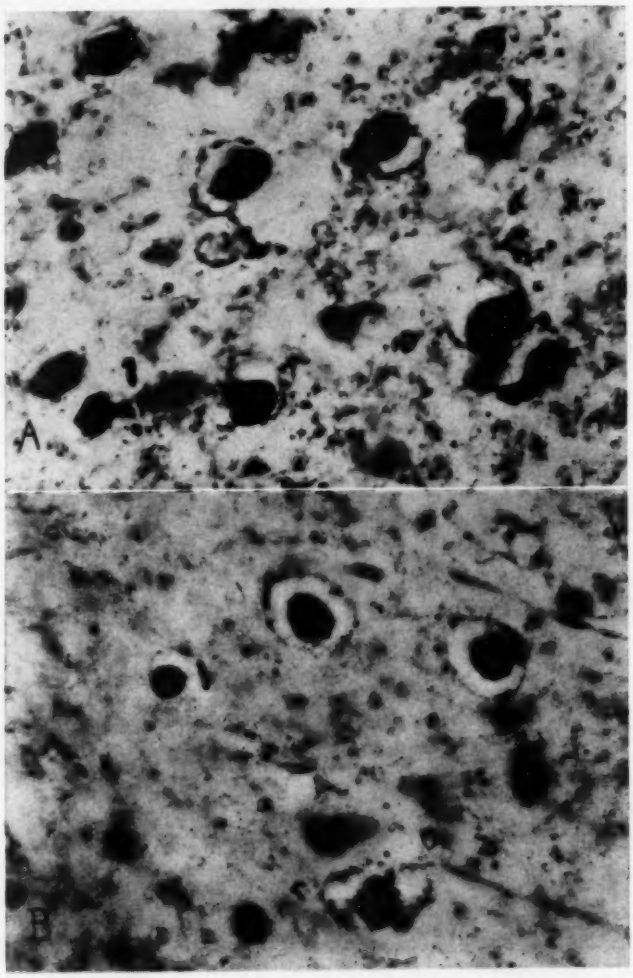

Fig. 20.—Swelling of the oligodendroglia in the brain with metastases from a primary carcinoma of the lungs (*A*) in the cerebral tissue close to the metastatic nodule; (*B*) in the edematous cerebrum at a distance from the metastatic nodule. Stain same as described under figure 19; × 850.

cases, the metastatic lesion was found in or near the motor area. Localizing signs were not definite in three cases. In one of these, a ventriculogram was made and a multicystic tumor was located. Subtemporal

decompressions were made in the remaining two cases and eventually the signs of a tumor manifested themselves, and metastases were removed at further operation.

Course of Illness: The course of illness was rapid in each case, so that the average period from the time of the onset of symptoms until hospitalization was but three months. One patient died one week from the onset of the intracranial symptoms, and two patients were ill for five months before being hospitalized.

Signs of increased intracranial pressure occurred early in the course of the illness in the majority of the patients. In ten of the eleven cases in which operation was performed, one metastatic nodule was removed, and in two instances a similar nodule was again removed from the same location after recurrence six months or a year later. In one patient no tumor was found. In this instance, the marked edema of the brain prevented a thorough exploration.

Five of the patients died within two weeks of the operation, and at necropsy the brains of four of these showed multiple metastases.

Four patients lived five months, seven months, two years and seven years after the operation, respectively, with complete relief from their intracranial symptoms until the final overwhelming spread of the disease followed by rapid death.

With the foregoing facts in mind, it is the opinion in this clinic that as a rule surgery is indicated in such cases, even though one is conscious that the lesion is a metastasis. For in instances in which the intracranial lesion was solitary, its removal with the leaving behind of the usual decompression has led to a prolongation of the patient's life and has spared him much suffering caused by an expanding intracranial lesion.

SUMMARY

Metastases to the central nervous system were found in fifteen of thirty-seven patients with bronchiogenic cancer. For eleven of the fifteen patients, a diagnosis of primary tumor of the brain was made, and the bronchiogenic tumor was overlooked. For the remaining four patients, a definite diagnosis could not be made.

An intracranial operation was performed on eleven of the patients, and a metastatic tumor was removed in ten instances.

The postoperative survival period of the patients with solitary cerebral metastasis varied from five months to seven years (case 5). An early postoperative fatality resulted in every patient with multiple cerebral metastasis.

It is believed that when a person of middle age has an abrupt onset of symptoms and signs of a rapidly developing intracranial lesion, a metastatic cerebral lesion should be thought of, and that the lungs are

the most common site of the primary lesion. It is realized, moreover, that even in instances in which the examination of the lungs yields negative results, the presence of a primary tumor in these organs cannot be excluded.

A metastasis to the brain from a primary pulmonary tumor was commonly mistaken for a rapidly growing glioma, a cerebral vascular lesion or an encephalitis.

Apparently, the pulmonary tumor metastasizes to the brain by way of the blood stream. The relatively great frequency of intracranial metastasis is due in all probability to the fact that a tumor embolus from a pulmonary cancer passes from the pulmonary vein directly into the cerebral circulation, whereas cancers from other viscera on their way to the brain are primarily retained by the lungs, where they may remain indefinitely, often being altogether destroyed.

There is an outstanding reaction on the part of the microglia and astrocytes to the metastatic lesion, the response being very much like that found in experimental studies on the reaction of the brain to wounds and to infectious invaders.

HEMANGIO-ENDOTHELIOMA OF THE LIVER*

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Relatively few cases of hemangio-endothelioma of the liver have been reported, and it seemed advisable to add this case to those already on record because of the difficulty of clinical diagnosis and the interesting pathologic picture. The case was that of an emaciated child 11 months old with a marked enlargement of the liver of unknown origin.

REPORT OF CASE

History.—A boy, 11 months of age, was brought to the hospital showing marked swelling of the abdomen of five months' duration. When the swelling was first noticed, the parents took the child to a physician, who prescribed quinine. The swelling continued, however, and there was no improvement. The patient was then brought to the dispensary, where it was found that the liver was enlarged and extended to 10 cm. below the costal border. The spleen was also enlarged and extended down to the same level. Both organs were smooth on palpation at this time. A few discrete, firm glands were palpable in the axillae and the neck. The child returned to his home in Damascus and received frequent injections of quinine with apparent benefit, but the swelling of the abdomen continued to increase rapidly. The child continued to nurse well, did not vomit or have diarrhea and only occasionally had fever.

The patient entered the hospital about two months after his visit to the dispensary. On physical examination, he was found to be fairly well developed and nourished. The abdomen was enormously distended, and a network of dilated veins was visible over the upper part of the abdomen. The lower edge of the liver was palpable 8 cm. above the symphysis pubis. The liver was covered with fluctuant nodules averaging 3 cm. in diameter. There was considerable fluid in the lower part of the abdomen. No tenderness or rigidity was elicited.

Laboratory Observations.—The red blood cell count was 2,840,000; the hemoglobin content (Tallqvist) was 60 per cent. The white blood cell count was 6,900. The differential count gave: polymorphonuclears, 68 per cent; lymphocytes, 30 per cent; monocytes, 1 per cent, and transitionals, 1 per cent. The Wassermann reaction was negative. The mother's Wassermann reaction was 1+.

Autopsy.—The body was that of a fairly well developed and poorly nourished male infant with a markedly distended abdomen. The skin over the abdomen was tense and shiny, and the umbilicus was everted. The liver was easily palpable, and the lower edge was felt at a point in the midline about 10 cm. above the symphysis. Multiple soft nodules could be palpated on the liver surface.

When the abdomen was opened, a large nodular liver was found occupying the entire right side. A liter (1,000 cc.) of clear yellow fluid was taken from the pelvis.

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The liver weighed 1,100 Gm. It was covered with purple nodules varying in size from that of a marble to that of a horse chestnut. These nodules stood out on a dull yellow background of liver substance, and were soft on palpation. Some were flat; others were umbilicated. On section, these dark red areas were found throughout the liver, replacing practically the entire organ (fig. 1). The small amount of liver tissue remaining was yellow. The nodules were hemorrhagic and were apparently surrounded by a band of white connective tissue.

The other observations at autopsy were enlarged mesenteric glands and a stone the size of the head of a pin in the upper part of the left ureter. No metastases of the tumor were found.

Histologic Examination.—Pieces of tumor and liver tissue were fixed in Kaiserling I solution, and were stained with hematoxylin and eosin and with van Gieson's connective tissue stain.

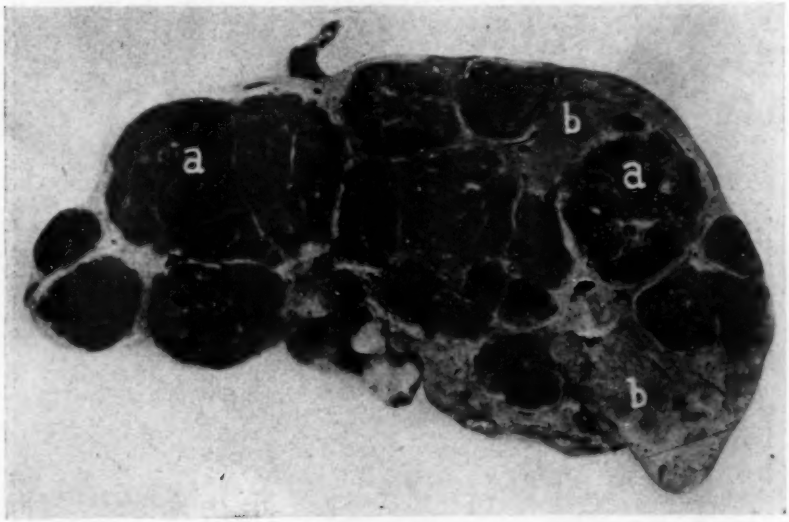

Fig. 1.—Liver showing: tumor nodules (*a*) and liver tissue (*b*).

Some tumor nodules were made up of dilated blood spaces separated by bands of connective tissue in which no liver cells were seen. The blood spaces were lined with endothelial cells, which appeared larger and more numerous than those of a normal blood vessel (fig. 2). The outlines of these cells could not be seen, but the nuclei stained a pale or deep blue and stood out against a pale pink cytoplasm. The nuclei were vesicular and oval or fusiform. No mitotic figures were seen. There was no evidence of hematopoiesis. The blood spaces were filled with red blood cells mixed with a normal number of leukocytes.

Other sections of the tumor showed a different picture. Under low power, the tissue appeared to be a solid mass of tumor cells with many tiny openings. Under high dry power, these tiny openings were found to be surrounded by single cells. These were apparently attempts to form blood vessels, for red blood cells were found in some of them. In many places were concentric blue-staining masses similar to those seen in dural endothelioma. Some fields showed small solid

masses of endothelial cells which had not formed blood vessels. The tumor nodules, in general, were found to be surrounded by connective tissue in which were a few atrophic liver cells.

A few foci of lymphocytes were found in the increased connective tissue around the bile ducts. The branches of the hepatic artery showed swelling of the endothelial cells. The liver cells showed albuminous degeneration, but were otherwise normal.

The diagnosis was congenital hemangio-endothelioma of the liver.

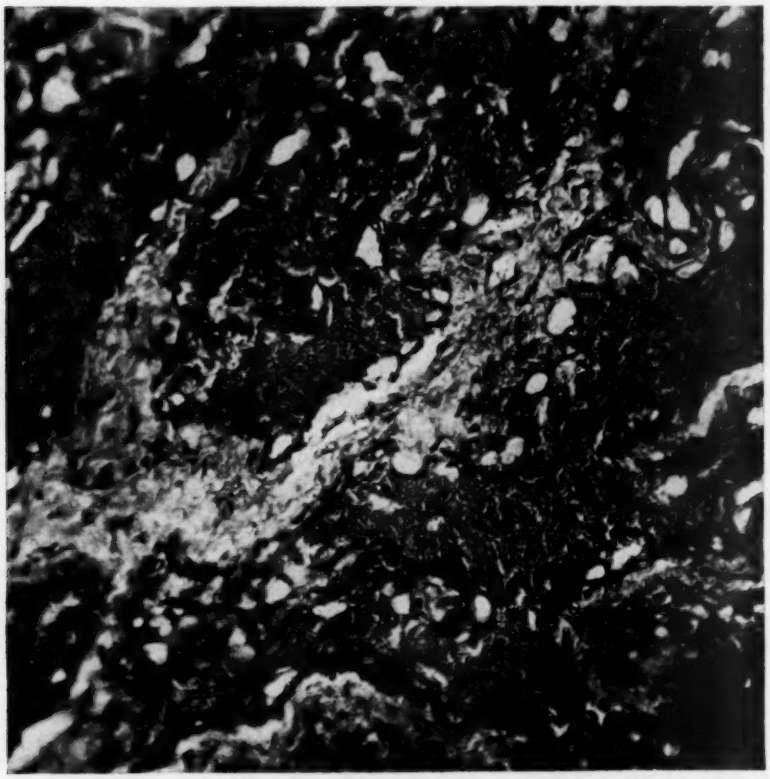

Fig. 2.—Section of tumor nodule showing blood spaces lined with endothelial cells.

THE LITERATURE

Foote [1] reported a case and reviewed the literature on congenital hemangio-endothelioma of the liver in 1919. He suggested that these tumors be called hemangio-endotheliosarcoma because they were the result of rapid and unrestrained proliferation of the endothelium of the capillaries of the liver. From the ten reports of cases which he reviewed, Foote concluded that such a tumor was a congenital disease,

1. Foote, J.: Hemangio-Endothelioma of Liver, J. A. M. A. **73**:1042 (Oct. 4) 1919.

manifesting itself by hepatic enlargement and some digestive disturbances within three months after birth. There was a fatal termination in every case before the patient was 6 months of age. The patient in the case described in this paper, however, lived until the eleventh month.

Foote [1] stated further that jaundice and ascites were not usually observed, and that metastases were not found. The liver was purplish and studded with nodules varying in size from that of a millet seed to that of an egg, some of which were confluent. These nodules were lighter in color than the surrounding tissue, and throughout the liver in cut section had in each instance a dark red center surrounded by a lighter colored ring. Histologically, the liver showed an infiltration of the normal areas with small round cells. In places, the liver cells were distorted, atrophied and vacuolated. The interlobular connective tissue was increased. The smaller blood vessels were choked with large endothelial cells, some showing mitotic figures. The nodules were surrounded by a fibrous band of compressed liver tissue. In some places, this fibrous band showed lacunae containing degenerated liver cells. The larger nodules were packed with large round or irregular cells with large nuclei, some areas resembling myxosarcoma. Giant cells and polymorphonuclears were also seen in some areas.

Gödel [2] described the condition of a child 3 months old with multiple primary tumors in the liver, which he diagnosed hemangio-endothelioma. The liver was 15 by 8 by 4.5 cm., and yellowish brown. Many nodules were seen through the capsule; they were the size of a hazelnut and smaller. On section, the nodules stood out bluish gray against the liver tissue. The microscopic picture was essentially the same as that reported in the liver here described.

Another case described by Orzechowski [3] differed in three particular features from any of the cases reports of which have thus far been published. The subject, a girl 2½ months old, was markedly icteric, and the liver parenchyma was greenish, indicating severe stasis of the bile. This hemangio-endothelioma had metastasized to the lung and to the skin, with multiple lesions in each organ. The third distinguishing feature was blood cell formation in the tumor nodules in the liver. This included the formation of both red and white blood cells and would indicate a continuation of the hematopoietic function of the liver from fetal life.

In none of the other cases reported in the literature thus far was icterus or hematopoiesis in the tumor of the liver observed. Hewlett [4]

2. Gödel, A.: Frankfurter. Ztschr. f. Path. **29**:375, 1923.

3. Orzechowski, G.: Virchows Arch. f. path. Anat. **267**:63, 1928.

4. Hewlett: Intercolon. M. J. Australia **4**:615, 1899.

was the only other author to report metastases from sarcoma of the liver in a case that may have been one of hemangio-endothelioma. He mentioned nodules in the lungs of the same general microscopic appearance as those in the liver, but he did not give the details of their structure.

Bondy [5] reported a case clinically which might be classified as one of hemangio-endothelioma. The child had a protuberant abdomen, especially in the right upper quadrant, which was first noticed by the mother when the child was 3 weeks old. The circumference of the abdomen at this time was 18 inches (45.72 cm.) at a point 1½ inches (3.77 cm.) below the costal border. Percussion over the upper three quarters of the abdomen gave a flat sound. On palpation, an indistinct mass was felt filling both sides of the upper part of the abdomen. The surface of the mass was smooth, and the edge was distinctly palpable below the umbilicus. This mass could not be definitely connected with any organ.

At operation, an enormously enlarged liver was found, filling three quarters of the abdominal cavity. The liver was dark brown and was mottled with small blue areas, averaging 1 cm. in diameter. The surface was smooth. The spleen and the kidneys were not enlarged, nor was there any invasion of any other organ. The child died at the age of 3½ months with a girth of 29 inches (73.66 cm.) at the umbilicus. No autopsy was permitted.

A piece of the liver was removed at operation, and the microscopic diagnosis was angiosarcoma. No description of the sections was given, so that one cannot conclude definitely whether or not the tumor fitted into the category of hemangio-endothelioma. The clinical picture, however, was similar to that in the cases thus far reported in the literature.

COMMENT

Various theories have been put forth in an attempt to explain the angiomas of the liver. Schmieden [6] believed that for the majority of such tumors, a simple dilatation of the capillaries affords an adequate explanation. Ribbert [7] also believed in the factor of capillary dilatation, but he maintained that this is secondary to embryogenic disturbances of the endothelium. I believe that in the case presented in this article the tumor was a true blastoma of endothelial cells. Some sections had the appearance of a simple cavernous hemangioma, while others had the appearance of an endothelioma. Mallory [8] stated that

5. Bondy, J.: Angiosarcoma of the Liver in an Infant, J. A. M. A. **56**:873 (March 25) 1911.

6. Schmieden: Virchows Arch. f. path. Anat. **161**:373, 1900.

7. Ribbert: Virchows Arch. f. path. Anat. **102**:351, 1898.

8. Mallory, F. B.: Pathology of Malignant Diseases of Nonepithelial Formation, J. A. M. A. **55**:1621 (Nov. 5) 1910.

tumors arising from endothelial cells should be called endotheliomas. Most pathologists, however, reserve this term for the rapidly growing tumors and speak of the slow-growing ones as angiomas. In another article, Mallory [9] proposed the name hemangio-endothelioma for those angiomas which show definite proliferation of endothelial cells and new formation of blood vessels.

Ewing [10] did not use the term hemangio-endothelioma of the liver. He called the tumor reported by Veeder and Austin [11] as hemangio-endothelioma, a multiple congenital hemangioma of the liver.

The sections of the tumor here described which show masses of endothelial cells indicate a more active and malignant tumor than the simple hemangioma which is seen in some of the sections in this case. It seems, therefore, that the term hemangio-endothelioma is correct for this tumor.

SUMMARY

A case of multiple congenital hemangio-endothelioma of the liver in a male infant 11 months old is described. The total number of such tumors reported in the literature to date is fourteen, including that described in this paper.

9. Mallory, F. B.: J. Exper. Med. **10**:575, 1908.

10. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 249.

11. Veeder and Austin: J. M. Sc. **143**:102, 1912.

VENTRAL SYMMETRICAL HYPEROSTOSES OF THE INNER TABLE OF THE CALVARIUM *

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CHICAGO

Occasionally, at autopsy, symmetrical thickenings of the inner table of the ventral portion of the calvarium are observed. These hyperostoses are more or less irregular in contour and are thickest within that portion of the frontal bones corresponding to the frontal eminences. The growths, when extensive, also involve parts of the adjacent parietal bones, but they characteristically avoid the orbital portion of the frontal bone and also the sagittal sulcus. They may be compact in structure or contain spongy diploe. The vascular channels are generally deep grooves or occasionally tunnels in the new bone. The high proportion of incidence in females is remarkable. The hyperostoses are symptomless and are rarely if ever diagnosed during life.

The literature of the last ninety years contains a number of references to this condition under various names. One of the early descriptions is in the catalog of the Musée Dupuytren [1] in which there are also three lithographic illustrations. There is minor mention of this type of hyperostosis by Bucknill and Tuke,[2] Birkett,[3] Clouston,[4] Lewis,[5] Humphrey,[6] Beadles [7] and Shattock.[8] Of greater interest are the con-

* Submitted for publication, Nov. 7, 1929.

* From the Norman Bridge Pathologic Laboratory, Rush Medical College.

1. Museum d'anatomie pathologique de la Faculté de médicine de Paris, ou Musée Dupuytren, Paris, Béchet jne. et Labé, 1842, vol. 2, pp. 503-505; atlas, pl. 15, figs. 5, 6 and 7.

2. Bucknill, J. C., and Tuke, T. H.: Manual of Psychological Medicine, Philadelphia, Lindsay and Blakiston, 1874, p. 567.

3. Birkett, J.: Contributions to the Practical Surgery of New Growths or Tumours: Series VI. Cartilaginous and Bony Growths, Guy's Hosp. Rep. (Series 3) **14**:475 (pl. 4, fig. 3) 1869.

4. Clouston, T. S.: Clinical Lectures on Mental Diseases, Philadelphia, Henry C. Lea's Son & Company, 1884, pp. 407-408; ibid., ed. 6, 1904, pl. 29.

5. Lewis, W. B.: Textbook of Mental Diseases with Special Reference to the Pathological Aspects of Insanity, London, C. Griffin & Company, 1889, p. 433.

6. Humphrey, G. M.: Senile Hypertrophy and Senile Atrophy of the Skull, Med. Chir. Tr., London **73**:327, 1890.

7. Beadles, C. F.: The Cranium of the Insane, Edinburgh M. J. (N. S.) **3**:263, 1898.

8. Shattock, S. G.: Morbid Thickening of the Calvaria; and the Reconstruction of Bone Once Abnormal; a Pathological Basis for the Study of the Thickening Observed in Certain Pleistocene Crania, Tr. Internat. Cong. Med., 1913, sec. 3, pt. 2; London, 1914, pp. 17-25, and pl. 3, figs. 1-5.

tributions by Rokitansky,[9] Naito and Schüler,[10] Naito,[11] Knaggs [12] and Stewart.[13] The most extensive studies are those by Engel,[14] Dressler [15] and Grieg.[16] In these writings there is reported a total of 165 instances of this abnormality of the frontal region. In 113 of the cases the patients were females and in 15 males. In 37 instances, the sex was not known. Dressler reported that in 1,632 autopsies, he found 71 of these hyperostoses or 4.35 per cent, 64 of which were in females and 7 in males. Grieg examined 188 calvaria, the sexes being practically equal, and found 32 with the hyperostoses, 28 being in females and 4 in males. Thus, in one large series, the incidence was over 4 per cent and of these nearly 90 per cent were in females.

In the museum of the Norman Bridge Laboratory of Pathology at Rush Medical College there are four calvaria bearing these hyperostoses.

No. 31.4-21.—This specimen is a skullcap (fig. 1) from an autopsy performed by Dr. E. R. LeCount on the body of a white man, aged 64, who died from chronic alcoholism and bronchopneumonia. It weighs 384 Gm. and is 18.9 cm. long, 13.7 across and 8 high. Externally, the contour is regular, and the suture lines are partly obliterated, the metopic suture entirely so. Wormian bones are present in the lambdoid and coronal sutures. An eburnated exostosis, 3 by 4 mm., and raised 0.5 mm., is present 1 cm. above the anterior sawed edge of the frontal bone 2 mm. to the right of the midline. There are delicate vascular grooves in the middle of either lateral half of the frontal bone from 0.5 to 2 cm. above the sawed edge. Minute vascular openings in the outer table are associated with these grooves.

Internally, all suture lines are obliterated, and the frontal region is covered by a bony thickening. The edge made by sawing measures 14 mm. at its thickest place in the right frontal region; in the left, 11 mm. In the occipital region, it averages usually about 4 mm. The contour of the hyperostoses medially is wart-like with small knobs and granules arising abruptly. The lateral portions are more regular in contour and come down gradually to the level of the rest of the inner table slightly beyond the coronal suture. The midline is avoided, so that ventrally

9. Rokitansky, C.: A Manual of Pathological Anatomy, Sydenham Society Translation, London, 1850, vol. 3, pp. 127, 129, 133, 211 and 378. This is a translation of the German edition of 1842.

10. Naito, T., and Schüler, A.: Ueber die Hyperostosen des Schädels, Wien. klin. Wchnschr. **36**:792, 1923.

11. Naito, Inasaburo: Die Hyperostosen des Schädels, Vienna and Leipzig, Josef Šafář, 1924, pp. 75-81.

12. Knaggs, R. L.: The Inflammatory and Toxic Diseases of Bone, New York, William Wood & Company, 1926, pp. 205-207.

13. Stewart, R. M.: Localized Cranial Hyperostosis in the Insane, J. Neurol. & Psychopath. **8**:321, 1928.

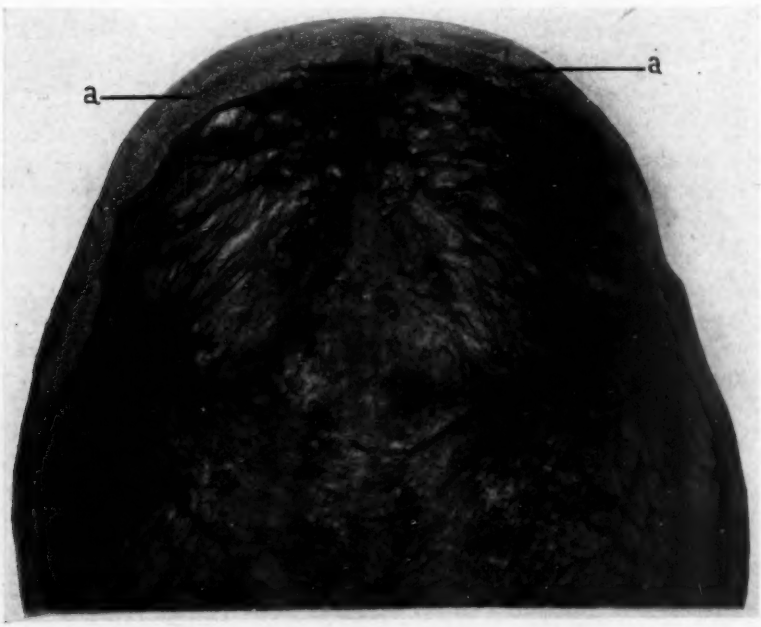
14. Engel, J.: Das Osteophyte an der inneren Schädelflache, Wien. med. Wchnschr. **21**:770, 794 and 823, 1871.

15. Dressler, L.: Ueber die Hyperostosen des Stirnbeins, Beitr. z. path. Anat. u. z. allg. Path. **78**:332, 1927. This contains a critical review of the literature, and the reader is referred to this article for additional references.

16. Grieg, D. M.: Intracranial Osteophytes, Edinburgh M. J. **35**:165 and 237, 1928.

at the sawed edge there is a narrow groove resembling a saw-cut, 1.5 mm. wide, flanked by steep sides 5 mm. high. At the surface, the groove is narrower, 1 mm., and at the bottom the walls are slightly undercut. The median free space widens out toward the bregmatic region, where it is 2.5 cm. wide. In the middle of this triangular free space is the shallow groove for the sagittal sinus and beside it depressions for the pacchionian bodies. The bregmatic region is no thinner than the nearby portions of the vault. The channels for the middle meningeal vessels are deep, particularly near the edge of the hyperostoses, and in places they become tunnels in the bone.

The surfaces of the hyperostoses are marked with elongated pits and fine wrinkles approximately parallel, but converging toward a point in the midline about 2 cm. above the ventral sawed edge. However, at the margins of the



The ventral portion of calvarium no. 31.4-21 illustrating the symmetrical hyperostoses of the inner table, the knoblike and the more diffuse portions of the growths, their avoidance of the midline, the inner boundary of the inner table (*a*) under the growths and the vascular furrows in the parietal regions.

growths, near the coronal suture, these streaks run in a coronal direction. The surface texture is smooth, almost polished.

Where the saw-cut passes through the hyperostoses, the compact outer table is from 1 to 1.5 mm. thick. Next is the diploe, a zone of spongelike structure, measuring about 2 mm. Then comes an ill defined compact layer slightly more than 1 mm. thick, evidently representing the original inner table, and this is followed by the hyperostosis. The latter is made up of a spongy layer as much as 8 mm. thick, slightly more porous than the normal diploe, and covered by a thin, hard layer, less than 1 mm. thick, forming the inner surface. At the edges of the growth, the innermost layer fuses with the inner table of the skull by disappearance of the spongy layer.

In the other three calvaria, concerning which there are no records, there is not as much adventitious bone.

No. 31.4-23.—This skullcap measures 18.7 by 14.1 by 8.3 cm. and weighs 542 Gm. Externally, all suture lines are distinct and a metopic suture is present. The skull is generally thick, and in the region of the vertex it measures 1 cm. The inner portion of the frontal region is humpy in contour, but the texture of the surface is smooth and hard. On the sawed edge, the thickest places measure 12 mm., on the right, and 10, on the left. The occipital region is about 6 mm. thick, though in the region of the internal occipital protuberance it is over 10 mm. thick. In the frontal region, the inner table is not traceable under the hyperostosis, but the area is uniformly spongy. The sagittal region is thinner than the frontal squamas.

No. 31.4-24.—This calvarium has all suture lines obliterated, except the coronal suture, which is present for about 2.5 cm. on the right and 4 cm. on the left between the superior and inferior temporal lines. It weighs 300 Gm. and measures 18 by 14.8 by 7.6 cm. Internally there is an increase in the thickness of the frontal squamas, so that the usual concavity there is made nearly flat, though gently undulating. There are four rounded knobs near the medial border of the left hyperostosis. The thickest place along the sawed edge on the left is 13 mm. thick; on the right, 8 mm. However, on the right, the saw-cut was below the main part of the hyperostosis. The midline is not thickened. The furrows for the middle meningeal arteries are deep and are converted into tunnels for short distances, 2 mm. on the left, 1.5 on the right. The rhomboidal bregmatic region is slightly thicker than the surrounding region and this impression is accentuated by the pits for the arachnoid granulations around it. The surface of the hyperostoses is smooth, except for fine striations.

No. 31.4-25.—This skullcap is 18 by 13.3 by 7.8 cm., in dimensions, and weighs 442 Gm. All suture lines are obliterated, except about 1.5 cm. of the coronal suture on both sides between the temporal lines. The specimen impresses one as unusually heavy. The edge is nowhere very thick, but the frontal concavities are filled with bone, presenting a wavy surface. The thickest portion on the left is 12 mm. thick; on the right, 11 mm. This thickening is diffuse, and the midline is not notably depressed below the level of either side. A depression for the main trunks of the middle meningeal vessels toward the bregma separates this region from pronounced thickenings of both parietal bones. These hyperostoses are irregular in outline and more irregular in contour than the frontal hyperostoses. The one on the right is 16 mm. thick; that on the left, 13 mm. Both drop off abruptly toward the midline and ventrally. Elsewhere, the edges slope down gradually to the surrounding level. A space from 2 to 3 cm. wide in the midline is not covered by these. There are deep grooves and in places tunnels in these growths for branches of the middle meningeal vessels. In the median longitudinal sulcus in the dorsal half of the parietal region, there are small irregular points and scales projecting a millimeter or so from the surface. The longest scale is 10 mm. long and 2 mm. wide. These appear to be delicately and superficially adherent to the underlying surface.

One of the earliest and most persistently repeated explanations of the etiology of these ventral hyperostoses is that by Rokitansky.[9] He suggested that the bone deposit is compensatory for atrophy of the

brain, either occurring in senility or occurring prematurely "as a consequence of mental diseases which are characterized by excitement." This point of view is elaborated by Engel,[14] and essentially similar opinions are expressed by Clouston,[4] Humphrey,[6] Beadles,[7] Shattock,[8] Naito and Schüler [10] and Naito.[11] Some of these, however, believe that hyperemia of the skull bones or dura is also an important factor and that this is brought about by such conditions as recurrent attacks of maniacal insanity or epilepsy. However, Grieg [16] reported that the mental condition of the persons represented in his series was "perfectly normal for the social position these people occupied during life." Lewis [5] thought that inflammation plays a part, and Knaggs [12] suggested explaining the hyperostoses on an inflammatory basis as arising from toxins, as he does pulmonary osteo-arthropathy. On the other hand, the absence of inflammatory change is attested by Dressler [15] and inferred by others. Theories based on disturbances of the endocrine glands are advanced for all sorts of diseased conditions, and Stewart [13] ventured that one may be "dealing with a hitherto undifferentiated type of dyspituitarism."

Grieg [16] approached the compensatory theory from a chemicophysiologic point of view and concluded that the hyperostoses are a result of disuse absorption of calcium and phosphorus from other parts of the skeleton in excess of existing excretory powers and that this excess is deposited in the frontal region as "an innocuous relief to a system supersaturated with calcium in an area which age renders least important."

Because there was no more than slight atrophy of the frontal lobes associated with any of the seventy-one calvaria studied by Dressler,[15] he was led to believe that a prolonged illness may cause the compensatory hypertrophy of the frontal bones by the dorsad sinking of the brain while the patient is confined to bed. He said that the midline is avoided in the new bone formation because the relations of pressure, in spite of the increased weight on the tentorium, do not affect the attachments of the tightly spread falx cerebri. He found long drawn out sickness in most of the histories.

The preponderance in females is missed by Engel,[14] but conceded by other observers. Beadles [7] thought it was due to the longer residence in the insane asylum by the female inmates. Dressler [15] attributed it to the earlier onset and more marked degree of atrophy of the brain in females with a possible temporary predisposition during pregnancies when, he supposed, there is a slight relative anemia of the brain and a "hormonal stimulus" that causes an increased proliferative reactivity of the bones. However, its occurrence in nulliparae, as well as in males, is emphasized by him and confirmed by Grieg.[16]

SUMMARY

Ventral symmetrical hyperostoses of the inner table of the calvarium are much more frequent in women than in men. There is a notable absence of full details of the illnesses which possibly may be associated with this overgrowth of bone. In the most attractive explanation so far advanced, compensation for atrophy of the brain in a "system supersaturated with calcium," many essentials needed to make it satisfactory are absent.

Historical and General Reviews

THE DETERMINATION OF THE INFECTIOUS NATURE OF ACUTE ENDOCARDITIS

IN COMMEMORATION OF THE FIFTIETH ANNIVERSARY OF THE CHICAGO PATHOLOGICAL SOCIETY

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AN EPISODE IN THE CHICAGO PATHOLOGICAL SOCIETY

On March 24, 1879, "Dr. Chris. Fenger, pathologist to the Cook County Hospital, exhibited some morbid specimens obtained from a recent patient. When he opened the body, the doctor had no history of the case, except that the patient presented typhoid symptoms. Opening the abdomen, he found infarctions in the submucous tissue of the intestines, in the spleen and in the kidneys. The source of these emboli was found in an ulcerous endocarditis, both sets of semilunar valves presenting an abundant deposit. Upon examining farther, an embolus was found in the left middle meningeal artery, which had caused an extensive infarct; and several small infarcts were found in each retina (illustrating the value of the ophthalmoscope in the diagnosis of heart disease). The doctor thought from the fact that some of the infarcts were breaking down into abscesses, that the cause of endocarditis was septicemia. There was no evidence of acute rheumatism nor of any surgical operation. Careful search, however, revealed a suppurating synovitis at the bottom of a large bunion. Dr. Fenger said this might have been the starting point of the whole disease. As a proof that this was a blood disease the doctor exhibited under the microscope some of the exudate from the heart valves in which were myriads of micrococci."

This report [1] was prepared by William T. Belfield, a pioneer American student of bacteriology. What interest has this report besides illustrating Fenger's power as pathologist? The report is remarkable because it is, if not the first, one of the first demonstrations in this country of the infectious nature of acute endocarditis. A brief résumé of the events that led to the establishment of the true nature of acute endocarditis will set forth the significance of Fenger's demonstration fifty years ago.

BOUILLAUD TO VIRCHOW

I shall not try to trace the earliest beginnings of knowledge about endocarditis. It begins with records and illustrations which show that the condition was observed at postmortem examinations. Many early observations of endocarditis are mentioned in the books; Cowper,

1. Fenger, Christian: Chicago M. J. & Examiner **38**:496, 1879.

Morgagni, Sandifort, Baillie and Alan Burns were some of the pioneer observers. The illustrations by Sandifort [1a] are striking, and his legends are precise, but he could not fully understand the lesion that he recorded. The connection between acute endocarditis and rheumatic fever, pyemia and other infectious states did not escape the notice of early observers. Morgagni, for instance, observed it in association with gonorrhea. But endocarditis remained a closed book until the nineteenth century. It was Bouillaud,[2] the great French clinician, who first pointed out clearly and comprehensively the anatomic and clinical characteristics of acute endocarditis. He set up two forms, the simple, frequently associated with acute articular rheumatism, and the typhoidal, in septic or putrid diseases. In the main this view has prevailed. Years passed before any new light was thrown on these conditions. In the meantime, the interest in the nature of suppuration and infection grew, and active search was made for the agents or poisons concerned.

In 1843, Vogel [3] described and figured "vibrios which develop in enormous numbers in all decomposing fluids, in decomposing blood, in decomposing eggwhite, etc., and which hardly ever are absent in foul ulcers." Vogel's figures will be referred to again. The word vibrio or vibrion is used frequently in early descriptions of microbes without the special meaning given to it later, but as synonymous with mobile bacterium. Somewhat later, vibrios, "Kugelbakterien," micrococcal masses and colonies, "granulations" were described as occurring in purulent and pyemic lesions. Mayrhofer claimed that puerperal infection was due to vibrios, which he found abundantly in the lochia. In 1879, Pasteur [4] said that he had seen streptococci ("petits chapelets de grain sphériques") in 1860. Rokitansky,[5] Oertel, Waldeyer, Rindfleisch,[6] von Recklinghausen, Klebs [7] and Orth [8] observed bacteria in human lesions. Apparently on the basis of the following statement,

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1a. Sandifort, Edward: Observationes antomico-pathologicae, Lugduni Batavorum, 1757.

2. Bouillaud, Jean-Baptiste: Traité clinique des maladies du coeur, etc., Paris, 1835; Traité clinique du rhumatisme articulaire et de la loi de coïncidence des inflammations du coeur avec cette maladie, Paris, 1841.

3. Vogel, Julius: Erlauterungstafeln zur pathologischen Histologie, 1843.

4. Pasteur, Louis: Bull. Acad. de méd. **81**:256, 1879.

5. Rokitansky, Carl: Lehrbuch der pathologischen Anatomie, ed. 3, 1855, vol. 1, p. 387.

6. Rindfleisch, Eduard: Lehrbuch der pathologischen Gewebelehre, 1867.

7. Klebs, E.: Weitere Beiträge zur Entstehungsgeschichte der Endocarditis, Arch. f. exper. Path. **9**:52, 1878.

8. Orth, Johannes: Untersuchungen über Puerperalfieber, Virchows Arch. f. path. Anat. **58**:473, 1873.

Rokitansky [5] has been given credit as the first to describe bacteria in endocarditis:

> Einmal habe ich runde, länglichrunde, 1/66-1/25 mill. im Durchmesser haltende, walzen- und wurstförmige, 1/33-1/25 mill. breite, bis zu 1/5 mill. lange, aus einem hyalinen in Essigsäure löslichen, eine Menge von kleinen bei Einwirkung von Essigsäure schrumpfenden körnchen einschliessenden starren Eiweisskörper bestehenden Gebilde, vereinzelt und zu Knäulen unter einander verschlungen, in Fibringerinnungen im Herzen bei Pneumonie, und ein zweiter mal ähnliche in fibrinösen Vegetationen an der Valv. bicuspidalis gesehen.
>
> This may be translated as follows: "Once in fibrinous clots in the heart in pneumonia and a second time in fibrinous vegetations on the bicuspid valve I have seen round, oblong (from 1/66 to 1/25 mm. in diameter), cylindric and sausage-shaped (from 1/33 to 1/25 mm. broad, up to 1/5 mm. long) formations of stiff, hyaline albuminous matter, soluble in acetic acid, occurring singly, as well as in twisted coils, and enclosing a multitude of small granules, which shrank under the influence of acetic acid."

Klebs [7] maintained that pyemia was caused by his *Mikrosporon septicum*, while diphtheritic (in the anatomic sense) processes were caused by a special fungus—a view to be opposed by Eberth.[9] Orth's description of chain-forming bacteria in the peritoneal exudate in peritoneal fever is particularly convincing.[8] It is well to recall that at this time special staining methods for bacteria were not available. The observations were made on unstained preparations after fat and other material had been removed by rather drastic methods. As example may be cited the statement by Orth as late as 1876 that there are numerous micrococcal colonies in ulcerative endocarditis which remain unchanged after boiling in absolute alcohol and ether followed by treatment with acetic acid.[10]

Of chief concern in this article is ulcerative or malignant endocarditis, the gross and microscopic changes of which were described accurately by the middle of the last century. The resemblance anatomically of the endocardial lesion in many cases to the so-called diphtheritic processes was recognized. The frequent association of ulcerative endocarditis with puerperal infection, with pyemia and with other infections was recognized fully, but its relation to these conditions and their lesions was not yet explained. A great advance was made when Virchow [11] completed his splendid doctrine of embolism and demonstrated in 1856

9. Eberth, C. J.: Zur Kenntnis der bacteritischen Mykosen, 1872; Cor. Bl. f. schweiz. Aerzte **2**:248, 1872; Ueber diphtherische Endocarditis, Virchows Arch. f. path. Anat. **57**:228, 1873; **65**:352, 1875; **72**:103, 1878.

10. Orth, Johannes: Compendium der pathologisch-anatomischen Diagnostik 1876.

11. Virchow, R.: Ges. Abhandl. z. Wissensch. Med. 1856, p. 705; Zur pathologischen Anatomie der Netzhaut und der Sehnerven, Virchows Arch. f. path. Anat. **10**:170, 1856.

the embolic nature of the arterial plugs in malignant endocarditis. In the next year, Beckmann [12] studied an instance of ulcerative endocarditis with capillary emboli in various organs. These emboli were minutely granular (äusserst feinkörnig). Apparently independently of Virchow, Kirkes [13] correctly interpreted the mechanical effects of the arrest in the circulation of solid particles detached from fibrinous deposits on the interior of the heart. Kirkes also had a notion that the general symptoms of ulcerative endocarditis were caused in some way by contamination of the blood by material from the diseased valves, and that consequently a poisoned state of the blood, analogous to pyemia, might result from ulcerative inflammation of the cardiac valves. A similar view was expressed by others at about this time. Watson,[14] after describing a case of ulcerative aortic endocarditis, said: "With such mischief in rapid progress within the heart, it is easy to see how the blood may be polluted and charged with a new poison in its very fountain."

Anatomically, ulcerative endocarditis resembles diphtheritic processes, said Friedreich [15] in 1861, and may discharge a specific ichorous substance ("specifische ichoröse Substanz") into the blood where it may exercise chemically infective actions on the organism with most pernicious effects and a pyemic, typhoidal symptom complex. In the rheumatic form, emboli have only mechanic effects.

Charcot and Vulpian [16] referred to certain minute particles in ulcerative endocarditis as having septic qualities and causing symptoms of intoxication. And Rindfleisch,[6] who saw vibrios in miliary abscesses in the myocardium, put it this way: "Various abnormal conditions of mixture of the blood, the pyemic, the puerperal, the typhoidal blood mixtures, above all the blood mixture in acute articular rheumatism, act upon the endocardium as inflammatory stimulus." Rindfleisch described the gross and microscopic changes in endocarditis adequately and interpreted their local consequences clearly.

The master mind now in charge of developments was, of course, Virchow. The results of his experiments and observations on embolism

12. Beckmann, Otto: Ein Fall von kapillar Embolie, Virchows Arch. f. path. Anat. **12**:59, 1857.

13. Kirkes, S. W.: Ulcerative Inflammation of the Valves of the Heart in a Case of Pyaemia, Edinburgh M. & S. J. **18**:119, 1853; Med.-Chir. Tr. **35**:281, 1852; On Ulcerative Inflammation of the Valves of the Heart as a Cause of Pyaemia, Brit. M. J. **2**:497, 1863.

14. Watson, Thomas: Principles and Practice of Physic, ed. 4, 1857, vol. 2, p. 315.

15. Friedreich, N.: Die Krankheiten des Herzens, in Virchow, R.: Handbuch der speziellen Pathologie und Therapie, 1861, vol. 5 (pt. 2), p. 322.

16. Charcot, J. M., and Vulpian, A.: Note sur l'endocardite ulcéreuse aigue de forme typhoide, Gazette méd., Paris **33**:386, 1862.

demanded explanation. Virchow himself at first thought that the suppuration in some instances of embolism was due to the chemical nature of the emboli themselves or of the subsequent changes in them. This general idea is reflected in some of the foregoing citations. Virchow also noticed mysterious minute glistening bodies in endocardial deposits and suppurative foci, thrombophlebitic as well as embolic. In puerperal endocarditis, the malignancy of the pyemic process was so much more intense than in simple endocarditis that something special ("etwas Besonderer") surely was at work, and he suggested that if the granules he had seen could be brought into etiologic relation to the endocardial lesion, the whole process might be explained.[17] The stage was fully set and waiting for the definitive demonstration of the microbic nature of endocarditis, and this demonstration fell to the lot of Winge and Heiberg.

WINGE'S DEMONSTRATION

In the transactions of the Norwegian Medical Society for 1869, page 78, occurs an untitled report that begins as follows: "E. Winge demonstrated a heart with a peculiar form of endocarditis from a man treated in the Rigshospital for pyemia." This heart (figs. 1 and 2) came from a laborer, aged 44, who was taken ill after the tearing out of a corn on the little toe, in the bed of which suppuration developed. Death took place twenty-five days later. The aortic valves presented large grayish vegetations, as did also in more marked form the tricuspid, and there were several ulcers with thrombotic deposits on the endocardium of the right side of the heart (figs. 1 and 2). There were fresh hemorrhagic infarcts in the left lung and two grayish-yellow infarcts in the left kidney, with softened thrombi in the corresponding arteries. In the endocardial vegetations (Hartnach, ocular 2, immersion lens; objective 9) were leptothrix chains (leptothrixkjeder) which were striated like a rosary or string of beads from the presence of short rods or round granules; in addition, there were many round or rounded bodies, partly bacteria, partly fat granules. Such bodies were found also in the emboli in the renal artery and in small foci in the myocardium, but not in the bed of the corn on the little toe. These bodies were not affected by acetic acid or by potassium hydroxide.

A rabbit was inoculated subcutaneously with material from the heart, but without apparent result. Winge's comments were brief: "It appears to concern a parasitic process; an external focus was present; acute endocarditis is a secondary pyemic process serving as a new focus

17. Virchow, R.: Ueber die Chlorose und die damit zusammenhängenden Anomalien im Gefässapparate, insebesondere über Endocarditis puerperalis, Beitr. z. Geburtsh. u. Gynäk. **1**:323 and 354, 1872.

Fig. 1.—Winge's case, 1869, tricuspid endocarditis. I am indebted to Prof. Francis Harbitz, of Oslo, for the photographs of this heart.

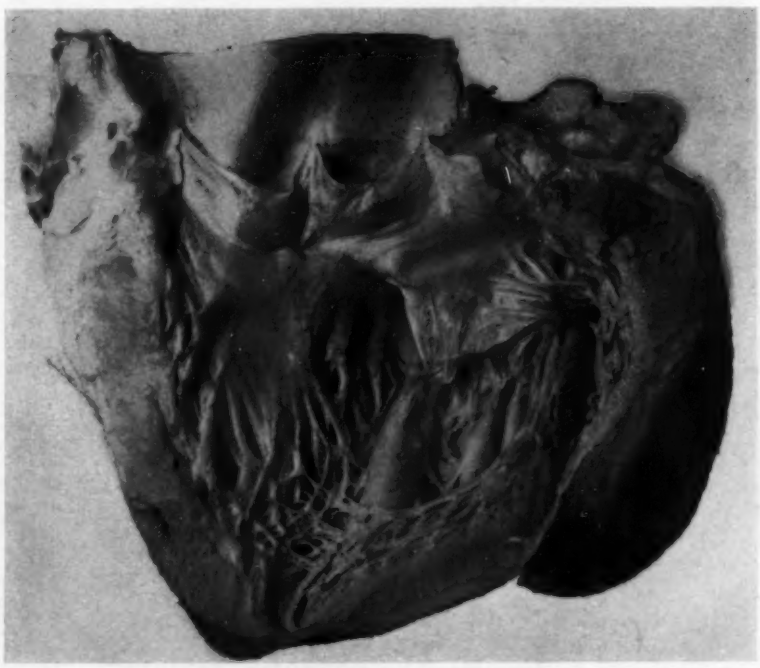

Fig. 2.—Winge's case, 1869, the left side of the heart.

for the distribution of microbes." Figure 3 shows that this case was one of streptococcus endocarditis.[18]

HEIBERG'S CASE[19]

This case occurred in a woman, 22 years old, following childbirth. There was an ulcerative mitral endocarditis, infarcts in the spleen and kidney, metastatic abscesses in the kidney, and thrombolymphangitis in the uterus. The masses in the heart contained numerous fine detritus-like granules between which were rod-shaped bacteria-like bodies and a number of larger and smaller rosary-like chains of granules. These were not attacked by alkalis. No chains were found in the infarcts of the spleen and kidney or in the uterus. The chains were like those described by Winge, but there were not so many bodies. Winge and Heiberg were closely associated, and Heiberg gave a full summary of Winge's case. He, also, inoculated rabbits without any result: Small bits of vegetations were placed in the peritoneal cavity, and in another experiment an unfiltered suspension of salt solution of the vegetation was given intravenously, death resulting immediately from convulsions.

Against the claim that the microbic invasion might have occurred after death, Heiberg urged that the examinations in both his and Winge's cases were made from twenty-five to thirty hours after death in cold weather, and that the bodies were well preserved, in Winge's case frozen stiff. Heiberg also referred to two museum specimens of ulcerative endocarditis in which he could not find any micro-organisms. He finally suggested that ulcerative endocarditis is due to infection from without and is pyemic in nature.

By their clear and simple reports, Winge and Heiberg completed the great work of Virchow and others on acute endocarditis in its relation to infection and pyemia.

Heiberg's description of the microscopic examination in his case reads as follows:

> On microscopic examination, the thrombus masses on the valvular ulcers and on the chordae show that they consist of numerous fine detritus-like granules,

18. Winge's report in Førhandlinger i det norske medicinske Selskab for 1869, p. 78, is not listed in the Index Catalogue, but in the first series, 1884, is listed a review of the report in Förhandlingar vid det Svenska Läkaresällskapets Sammankomster, 1870, p. 172. An abstract by Winge himself occurs in Nord. med. Arkiv., 1870, vol. 2, article 14, p. 15. There is a good abstract, entitled Mycosis Endocardii, in Canstatts Jahresbericht (**2**:95, 1870). And Heiberg's article (Virchows Arch. f. path. Anat. **56**:407, 1872) also contains the essential details.

19. Heiberg, Hjalmar: Ein Fall von Endocarditis ulcerosa puerperalis mit Pilzbildungen im Herzen (Mycosis Endocardii), Virchows Arch. f. path. Anat. **56**:407, 1872; Forh. norske med. Selskab, 1872, p. 60, and 1873, p. 72; Die Puerperalen und pyämichsen Processe, 1873.

between which are numerous more rod-formed, bacteria-like bodies and a considerable number of rows of granules arranged in shorter and longer roset-like chains, which represent leptothrix chains. There is no distinct fibrin, but rather many white blood corpuscles in the thrombus mass. On addition of potassium hydroxide and even on boiling with it, the leptothrix chains are not attacked, and many of the finer granules also remain, although most of them are destroyed by the alkali. In the infarcts observed in the kidney and spleen and the afferent arteries, detritus-like granules could be demonstrated, but no chains. Nor were any found in the thrombotic lymph vessels on the left margin of the uterus or on the inner surface of the uterus. The chains, which in respect to length and

Fig. 3.—Photomicrograph of section made by Prof. Francis Harbitz, Oslo, in 1929 of endocardial vegetation in Winge's case; gram stain; × 2,000. Photomicrograph reproduced by courtesy of George R. Callender, Major, M.C., U.S.A., Army Medical Museum, Washington, D. C.

size of the individual members correspond with those in the heart in Winge's case, which is still preserved in the museum here, cannot easily be confused with disintegrating thrombus masses, which, of course, naturally would be thought of first, under the circumstances, because of the regularity and the equal size of the granules, or members, which resist boiling alkali. It is true that occasionally one sees in disintegrating thrombi two, three or four definite detritus granules in a row, but the individual granules always vary in size and one never finds—as in the leptothrix chains now described — from ten to twenty connected members.

Heiberg's comment on Virchow's work on endocarditis is interesting:

> On postmortem examination of a young officer, Virchow found numerous vibrios and fungus-like formations in the pulmonary veins, which were regarded as postmortal, but the point is that "in the finer cerebral vessels there were found, in addition, numerous colorless cells and here and there similar densely crowded accumulations of very small granules." In Virchow's case of puerperal endocarditis were found peculiar granules set into a somewhat hyaline matrix, "a diphtheritic mass." Virchow assumed "that in the blood itself may be distributed parts of this kind, which multiply in the blood and possess the possibility of striking root on the endocardium and of spreading farther"; "that germs are present intra vitam, which multiply post mortem." The thought of fungi or bacteria must have been before him, but it would be hazardous to conclude from the presence of mere granules that it concerned bacteria or micrococci. We would not have concluded that it concerned fungous formations if we had not found granules in chains.

According to a note by Virchow at the end of Heiberg's report, pieces of both the hearts were sent to him, and he found the bodies

Fig. 4.—"Vibrios," figured by Vogel in 1846. Virchow said that the small bodies in Winge's case resembled these vibrios.

described. He questioned whether they should be called "leptothrix-ketten" rather than vibrios. The granular mass left after treatment with acetic acid or alkali consisted of dense accumulations of fine granules, the parasitic nature of which he did not question. He said that in Winge's case, small roundish bodies formed long chains like chains of pearls, resembling the vibrios described and illustrated by Vogel (fig. 4). These bodies did not resemble *Leptothrix*. Virchow noted that a principal argument for the diagnosis, namely, the mobility of the granules and chains, could not be advanced by him because he had before him only alcoholic preparations. He went on to say: "I know from other experiences how difficult it is to reach a conclusion in regard to such minute bodies, and this is also the reason why I expressed myself carefully in my contributions on puerperal endocarditis. That it concerns parasitic processes I nevertheless have said definitely and their relation to diphtheritis and to infection of the blood I have expressed in this sense."

EMANUEL WINGE AND HJALMAR HEIBERG

Emanuel Winge, 1827-1894, passed his state medical examination in 1851. After a few years in various temporary positions, he spent a year of study in Berlin, Prague, Vienna and Paris, giving most of his time to pathologic anatomy and chemistry under Virchow and Hoppe-Seyler. In 1858, he became prosektor in the newly established pathologic institute in Oslo (then Christiania), and in the winter of 1858-1859 he again studied pathologic anatomy in Berlin, passing also some time in Holland and England. In the fall of 1859, he accompanied Virchow on a journey in Norway to study leprosy. In 1866, he became professor of pathology, the first such in the Norwegian university, and in 1869 he was appointed professor of internal medicine. While he was professor of pathology, his assistant was Hjalmar Heiberg, who succeeded him as professor. Together they studied the preparations on which Winge's report on acute endocarditis is based.

Winge's best published work dates from the period he worked in pathology. In 1863, he published an important article on changes in the internal organs in syphilis. He was an able and conscientious man, painstaking and thorough in his work, greatly respected on all sides, successful and influential in his teaching over a long period, in which he emphasized the importance of pathologic anatomy. He has been characterized as "the pathological anatomist at the bedside."

Hjalmar Heiberg, 1837-1897, studied pathologic anatomy in Würzburg and Vienna. In 1870, he succeeded Winge as professor of pathology and continued as such until his death. He was a master teacher—"the clinician at the postmortem table." His remarkably comprehensive grasp of pathologic problems is illustrated in his report on endocarditis and especially in his short monograph on "Die puerperale und pyaemische Processe," 1873, which is a pioneer piece of work of fundamental significance in bacterial pathology. It is a classic that deserves to be known better than it is. Here Heiberg said that his attention was led to the relation of bacteria to ulcerative endocarditis and pyemia by Winge's case in 1869. Subsequently, he studied a series of such cases, including the case he reported in Virchow's *Archiv* in 1872.[19] His technic was simple indeed: unstained, double-knife sections in potassium hydroxide. On page 16, he clearly described what later was included under myocardial segmentation. He made it clear that only a minute lesion of the surface is required for the entrance of bacteria into the body, but whether every case of ulcerative endocarditis results from pyemia cannot be said. He traced the course of the bacteria in certain cases, e. g., puerperal infection, through lymph vessels and veins to the heart and from the heart into metastatic foci, and finally even into the urinary tubules. He was thoroughly familiar with the literature and referred to Pasteur's and Lister's work as revolu-

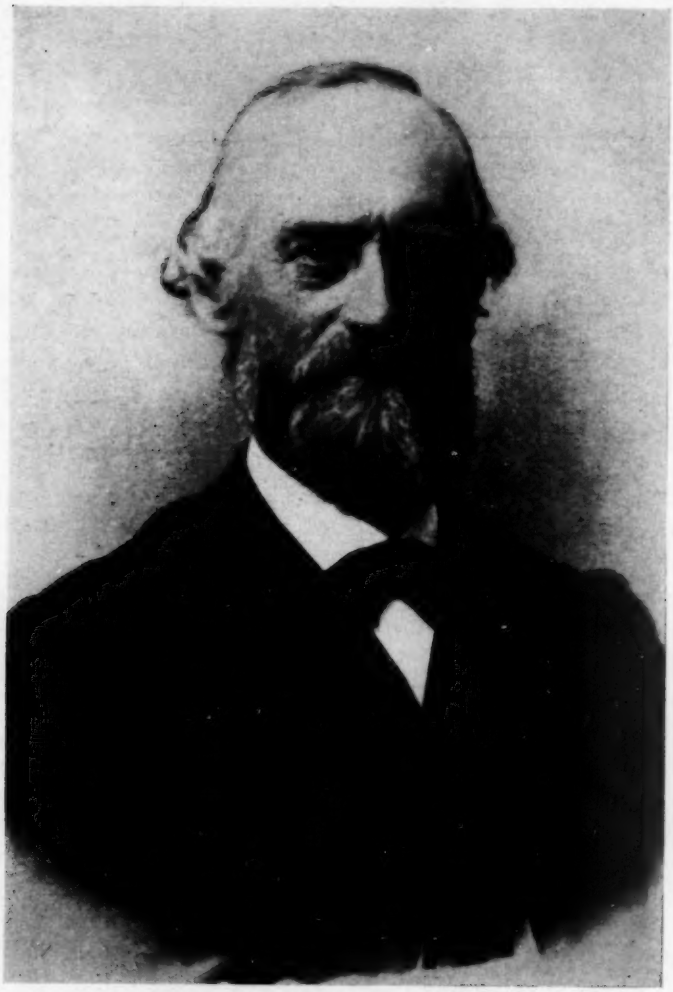

Fig. 5.—Emanuel Winge (in 1890).

tionizing. He raised the question whether the bacteria are specific and how they are transferred. Is there a spontaneous pyemia? In answer, he stated that ulcerative endocarditis does occur without demonstrable wounds, but in such cases how can infection through the nose, trachea or lungs be excluded? And are not the accessory nasal sinuses danger-

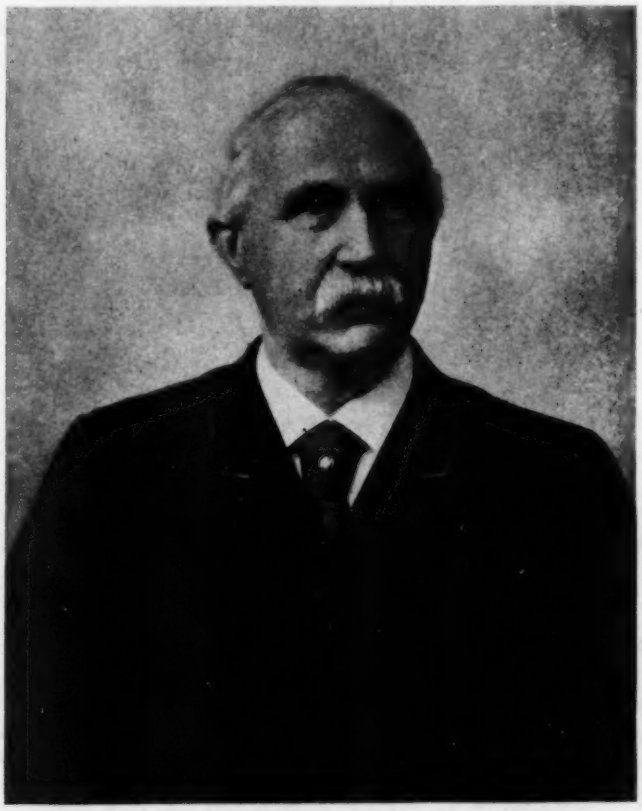

Fig. 6.—Hjalmar Heiberg.

ous possibilities? Finally, let me quote a foreshadowing statement of special interest: "If one considers the properties of protoplasm and the ameboid cells, which often enough wander in between the epithelium from the mucosa, there is a priori nothing in the way of the assumption that even corpuscular elements, e. g., bacteria, may be taken up by the epithelium and then spread themselves farther in the mucosa and thence along the lymph vessels."

THE INTERVAL BEFORE THE PERIOD OF CULTURAL AND EXPERIMENTAL METHODS

Immediately following Winge's and Heiberg's reports, confirmatory observations began to be recorded. Eberth,[9] for instance, was practically synchronous with Heiberg in 1872. Eberth described micrococcal masses in the vegetations of acute endocarditis and in pyemic abscesses. From the circumstance that the bacterial masses frequently are loosely deposited without noteworthy valvular involvement, he assumed that the bacteria are deposited from the blood and gradually work their way into the valve.

Klebs,[7] Larsen,[20] Burkart,[21] Eisenlohr,[22] Fleischhauer,[23] Gerber and Hirschfeld,[24] Maier [25] and Rosenstein [26] described cases in support of and illustrating the view that endocarditis is infectious. Lancereaux in 1873 accepted a puerperal form of endocarditis, but in 1881 he apparently doubted whether the facts at hand were sufficient to establish the parasitic nature of acute endocarditis as claimed by Winge and Heiberg. Others, like Hiller, denied offhand that acute endocarditis could be infectious. Many of these reports have good illustrations.

In 1876, Rosenstein [26] wrote as follows: "In a small but well attested series of cases these substances ('granular masses') have been proved with certainty to consist of parasitic organisms of the micrococcus genus (Winge, Heiberg, Burkardt, Eisenlohr)."

In 1878, Koester [27] on the basis of recorded observations and his own concluded that acute endocarditis is a micrococcal and embolic process and itself a depot for further embolic processes. He pointed out that in all cases, except Winge's, the bacteria observed in acute endocarditis were described as micrococci, micrococcal colonies, micrococcal masses, etc., and that such forms undoubtedly had been seen by Rokitansky (1855) and by Virchow (1856). Rokitansky [5] saw finely

20. Larsen: Om ondarted Endokardit, Norsk Mag. f. Laegevidensk. **3**:279, 1873.

21. Burkart: Ein Fall von Pilzembolie, Berl. klin. Wchnschr. **11**:149, 1874.

22. Eisenlohr, C.: Ein Fall von ulcerativer Endocarditis mit Micrococcusembolien, Berl. klin. Wchnschr. **11**:389, 1874.

23. Fleischhauer, J.: Akuter Gelenkrheumatismus mit multiplen miliären abscessen, Virchows Arch. f. path. Anat. **62**:386, 1875.

24. Gerber and Birch-Hirschfeld: Ueber einen Fall von Endocarditis ulcerosa und das Vorkommen von Bakterien in dieser Krankheit, Arch. d. Heilkunde **17**: 208, 1876.

25. Maier, R.: Ein Fall von primärer Endocarditis diphtheritica, Virchows Arch. f. path. Anat. **62**:145, 1875.

26. Rosenstein, S. S.: Encyclopaedia of the Practice of Medicine, edited by H. von Ziemssen, American editor, Albert H. Buck, 1876, vol. 6, p. 66.

27. Koester, K.: Embolische Endocarditis, Virchows Arch. f. path. Anat. **72**:257, 1878.

granular masses, the nature of which he did not specify, and Virchow referred to similar structures and their possible parasitic nature.

In this country, it was several years before the significance of the new views of acute endocarditis was noticed. Except for the statement in von Ziemssen's "Encyclopedia," [26] the first mention of the new departure appears to have been in 1878, when Keating,[28] in describing a case of ulcerative endocarditis with pyemia, cited Lancereaux (1873) as quoting the observations of Winge and Heiberg, verified in one case by Virchow, in which "vibriones of filiform shape were found in the ulcers." "If the germ theory be accepted, the emboli may be charged with bacteria," he said.

In 1879, Loomis [29] reported to the New York Pathological Society that he had found bacteria in the lesions in a case of pyemia. A discussion followed on the question "whether the bacteria found were the cause or the effect of the pathological changes, but as no conclusion was arrived at, the society went into executive session." In 1880, Peabody [30] in the same society spoke of finding micrococcal masses in the vegetations, the valve substance and the renal vessels in ulcerative endocarditis. The following year Osler [31] showed the society microscopic preparations from endocardial vegetations containing minute bodies, corresponding to bacteria, and resisting acids, alkalis, ether and chloroform. In the discussion, Alonzo Clark and Satterthwaite denied that these bodies had any pathogenic significance. Clark raised the question how such bodies could enter from without, and Satterthwaite held that they had entered after death; and Osler himself seemed to be inclined to view them as concomitants rather than the real materia morbi.

In 1881, Garland [32] reported an instance of ulcerative aortic endocarditis in the yellowish-white deposit of which were small white specks "composed of minute round bodies (micrococci)." He gave probably the best American review of this period on infectious endocarditis:

> The nature of ulcerative endocarditis has long been the subject of discussion and experimentation. Virchow detected, many years ago, a difference between this and ordinary endocarditis. Seeking an explanation of this difference, he cut

28. Keating: M. & S. Reporter **39**:206, 1878; Tr. Coll. Phys. Philadelphia **4**:27, 1879.

29. Loomis: M. Rec. **17**:42, 1880.

30. Peabody, G. L.: M. Rec. **18**:131, 1880; Bull. New York Path. Soc. **1**:207, 1881.

31. Osler, William: Infectious (So-Called Ulcerative) Endocarditis, Arch. Med. **5**:53, 1881; On Some Points in the Etiology and Pathology of Ulcerative Endocarditis, Tr. Internat. M. Cong. **1**:341, 1881; Ulcerative Endocarditis, M. Rec. **19**:245, 1881.

32. Garland, G. M.: Ulcerative Endocarditis, Boston M. & S. J. **104**:434, 1881.

up various substances and injected them into the veins of an animal. Bits of caoutchouc simply produced the ordinary results of mechanical obstruction to the circulation, while animal substances (bits of muscle, fibrin, etc.) caused severe inflammation, suppuration, and sloughing. Virchow therefore concluded that the phenomena of infection were due to chemical changes in the emboli. Others followed this idea in assuming that the irritant effects are due to the decomposition of the emboli which plug the vessels. Lancereaux thought the poisoning was caused by an alteration in the connective tissue of the valves themselves, and not by disintegration of the vegetations alone. Virchow noticed that the valvular deposits contained fine closely packed granules, which were insoluble in potash, acetic and hydrochloric acids, but were dissolved in chloroform. He considered them to be of a fatty nature.

Professor Winge was the first one (1869) to advance the theory that these granules are living organisms, and he called the disease mycosis endocardii. This same view was taken by Professor Heiberg, of Christiania, who sent specimens to Virchow for examination. With further study Virchow, Klebs, Köster, and a number of other Germans have given their approval to this theory, and they say that the organisms found are micrococci, vibriones, bacteria, and leptothrix filaments. Some of these observers believe that the germs are the essence of the disease. Heiberg inclines to the germ side of the question, but he allows that cases of ulcerative endocarditis present themselves wherein no parasites can be detected. Eberth thinks that the bacteria are introduced into the blood from without, and become aggregated into a sticky mass, which adheres to the surface of the cardiac valves. Here they multiply rapidly, and, dropping off, are distributed to all parts of the body. On the other hand, some writers repudiate the germ theory with great vigor, and claim that the parasites, if present, are merely the accidents of the disease. Hiller says that bacteria and leptothrix are constantly present in the healthy mouth, and if they are so dangerous we ought to be poisoned all the time. He thinks the granules decribed are merely detritus.

Osler wrote on acute endocarditis several times, first in 1881. In his first contributions,[31] he is rather disappointing, largely because he was not fully familiar with the literature of the previous decade. He found what he thought were micrococci in all the cases that he examined. In his Gulstonian lectures[33] on malignant endocarditis in 1885, he was fully abreast with his time and urged the study of cultures from the vegetations, particularly in so-called simple endocarditis, and that consideration be given to the possibility of the experimental production of endocarditis. In 1908, he wrote: "The infective character of endocarditis has only been fully recognized since the studies of Winge, Köster and Heiberg."[34]

In 1879, Park,[35] then in Chicago, pointed out that in ulcerative or diphtheritic endocarditis micrococci form a prominent element; embolic

33. Osler, William: The Gulstonian Lectures on Malignant Endocarditis, Brit. M. J. **1**:467, 1885.

34. Osler, William: Acute Endocarditis, in Osler and McCrae: Modern Medicine, ed. 1, Philadelphia, Lea & Febiger, 1908, vol. 4, p. 133.

35. Park, Roswell: A Conspectus of Three Different Forms of Acute Inflammatory Cardiac Disorder, Chicago M. J. & Examiner **39**:349, 1879.

infarctions with consequent abscesses frequently develop, the emboli acting as "infective excitants." In the vegetative or subacute form of endocarditis, on the other hand, micrococci are not found, the action of emboli in such cases being mechanical and not infectious.

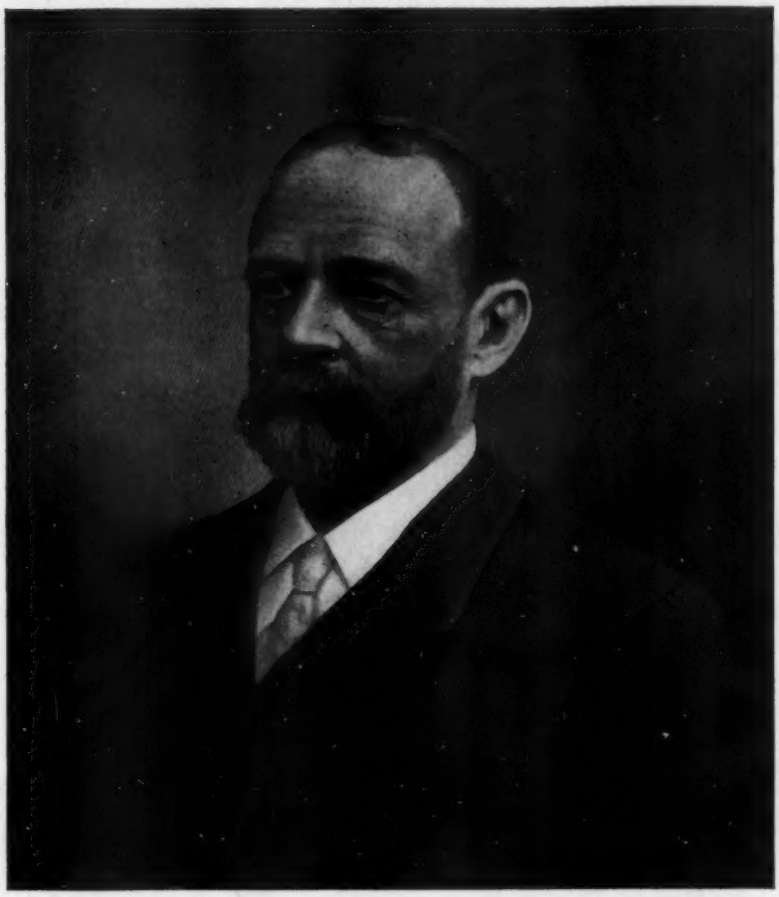

Fig. 7.—Christian Fenger, 1840–1902.

From this review it is evident that Fenger's demonstration before the Chicago Pathological Society fifty years ago is worthy of special recognition as a pioneer demonstration in this country of the infectious origin of acute endocarditis.[1]

The next phase in the development of the knowledge of acute endocarditis is the study of its causative bacteria by cultural methods and of

its experimental production. I shall not go into this phase, except to mention Prudden's [36] work on experimental endocarditis mainly because of his comprehensive grasp of the work with which we have been dealing. Winge, he said, formulated for the first time a consistent theory of acute endocarditis, based on careful observation and the assumption that microbes may be transported from external foci through the veins to the heart, where they produce the lesions by lodgment on the valves.

36. Prudden, T. M.: An Experimental Study of Mycotic or Malignant Ulcerative Endocarditis, Am. J. M. Sc. **93**:55, 1887.

THE INTRACELLULAR "SYMBIONTS" AND THE "RICKETTSIAE"

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PRINCETON, N. J.

(Concluded from p. 96)

THE "RICKETTSIAE"

The intracellular micro-organisms of arachnids and insects have interesting pathologic affinities through the various so-called "rickettsiae."

The problems of the "rickettsiae" received an impetus during the World War, when insects, especially lice, played such an important rôle in the transmission of disease and in the production of epidemics among the troops of the various nations. Since the war, the interest in the subject has abated somewhat; however, many workers have continued to contribute valuable information and have extended the work not only in man, but in domestic animals and in invertebrates.

The genus *Rickettsia* was erected by da Rocha-Lima in 1916 for certain minute micro-organisms found in the human body louse (*Pediculus humanus*) infected with the virus of exanthematic typhus fever. These micro-organisms had been seen previously by Hegler and by von Prowazek, but the generic name was chosen to honor Howard Taylor Ricketts, a martyr to the investigations of typhus fever pursued in Mexico City in 1910. Some writers believe that Ricketts first observed members of this group, but without completely interpreting their significance. Da Rocha-Lima designated the species "prowazeki" to aid in perpetuating the memory of von Prowazek, the capable investigator, also sacrificed in the work on typhus fever. Since 1916, *Rickettsia prowazeki* has become the type species for all subsequent researches on a group of micro-organisms segregated from established classifications.

Töpfer (1916) found a form of rickettsia, *R. wolhynica* (*R. quintana*), in body lice collected from soldiers afflicted with trench fever. Some observers, for example, Bacot (1921) and Wolbach, Todd and Palfrey (1922), thought this form the same as *Rickettsia pediculi*, which Munk and da Rocha-Lima (1917) considered a nonpathogenic normal parasite of lice. Sikora (1921) seems to have further established the probability, however, that *Rickettsia pediculi* is a separate species from *R. wolhynica* (*R. quintana*).

In 1917 and 1919, Wolbach greatly extended the work of Ricketts on Rocky Mountain spotted fever. Wolbach found an interesting

and extremely pleomorphic micro-organism invariably associated with the disease. It is highly probable that Ricketts observed one of the forms in which the parasite reveals itself, but was unable to bring order out of the confusing facts that the problem presents. Wolbach, however, felt that the various forms found were genetically related and merely represented different stages of an extremely pleomorphic rickettsia. This author erected a new genus and named the Rocky Mountain spotted fever parasite *Dermacentroxenus rickettsi,* the generic name being derived from the disease transmitter discovered by Ricketts, namely, the wood tick *Dermacentor venustus* (andersoni).

In 1923, Sellards reported the discovery of another form of rickettsia in Japan, which he felt was associated with the "Japanese flood fever," tsutsu-gamuchi disease, transmitted by the bites of infected mites, *Trombicula akamuchi.* Sellards named the micro-organism *Rickettsia nipponica.*

The fifth pathogenic rickettsia described to date is *Rickettsia ruminantium,* discovered by Cowdry in 1925. This micro-organism, according to Cowdry, is the cause of a serious condition, heart-water disease, in sheep, goats and cattle in South Africa and is transmitted by a tick, *Amblyomma hebraeum.*

Recently, Sellards and Siler (1928), while working on dengue fever in Manila, found rickettsiae in infected specimens of the transmitter of mosquito disease, *Aëdes argenteus* (*aegypti*). These writers were extremely conservative; however, from their work, it seems likely that a causal relationship exists between the micro-organisms found and the disease.[7]

The foregoing enumeration to date comprises the entire list of diseases due to so-called rickettsiae transmitted to man and the higher animals. Much more work, however, has been accomplished with various arachnids and insects in determining the distribution of supposedly nonpathogenic rickettsiae among them, their introduction into and localization within the invertebrate host and their differentiation from the pathogenic forms. Aside from any biologic interest that such work may present, it is important also from the medical point of view, because, as is well known, many arachnids and insects are either actually or potentially capable of transmitting parasites and infectious diseases.

7. Megaw and Rao (1928) showed that in many places in India sporadic typhus-like fevers occur of which the vectors are entirely unknown. Most of these fevers strongly suggest transmission by an arthropod from a rodent reservoir, and the authors consider it desirable that these diseases be investigated with special reference to ticks, mites and other forms. They also think it perfectly possible that a typhus virus might be conveyed by two alternative arthropods, especially by the louse and the tick.

The most extensive general surveys for rickettsiae in arthropods were those made by Cowdry (1923, 1925) and by Hertig and Wolbach (1924). Other workers, such as Nöller (1917, 1920), Sikora (1918, 1921), Arkwright, Atkin and Bacot (1921) and Noguchi (1926), have also contributed. In all, between thirty and forty different forms of rickettsiae have been described as occurring in such a variety of forms as mites, ticks, *Mallophaga* (biting lice), *Siphunculata* (sucking lice), bedbugs, beetles, sandflies, mosquitoes, horse flies, pupipara (keds) and fleas.

Woodcock (1922, 1923) thought that all rickettsiae in human and mammalian tissues and in insects were cell granules, artefacts or débris. Other investigators considered the pathogenic and non-pathogenic rickettsiae small micro-organisms distinct from bacteria. Da Rocha-Lima (1916), Jungmann (1916) and Sikora (1918) thought that they were closely related to the "strongyloplasmata" of Lipschütz and to the "chlamydozoa" of von Prowazek (Sikora, 1921). However this may be, Cowdry's recast definition, of 1926, is probably accepted at present by many workers. This author defines the rickettsiae as: "Gram-negative, bacterium-like organisms of small size, usually less than half a micron in diameter, which are found intracellularly in arthropods, which may be more or less pleomorphic and stain rather lightly with aniline dyes, but which resemble in most of their properties the type species, *Rickettsia prowazeki*."

The coccoidal forms of *Rickettsia* may measure less than half a micron in diameter (*R. prowazeki, R. wolhynica, R. ruminantium*). The spherical forms of *R. melophagi* of the sheep ked measure from 0.4 to 0.6 microns in diameter, and the rods from 0.3 to 0.4 microns in width by from 0.5 to 0.6 microns in length. The bacillary form of *Dermacentroxenus rickettsi* is larger, measuring from 0.5 to 1 micron in length, whereas the filamentous forms of the rickettsia of the bedbug (*R. lectularia*) may attain a length of from 3 to 8 microns. The type species (*R. prowazeki*) and some others are smaller than most bacteria, but, as shown, the minute size usually emphasized has exceptions.

The rickettsiae often occur as cocci or diplococci, as lanceolated or short and longer straight and curved bacillary forms and filamentous species, especially within the invertebrate host. The various forms are often arranged in pairs, end to end, and frequently one finds a longer form paired with a shorter or bud form. In general, the rickettsiae described are extremely pleomorphic, but it seems probable that some structures observed are not always genetically related. One need merely recall the interesting monosymbiotic, disymbiotic and trisymbiotic relationships that exist in many insects. This possible confusion is difficult to avoid, however, until more of the micro-organisms, under considera-

tion, have been isolated and studied in pure cultures. Notwithstanding, good evidence appears to exist in favor of cases of extreme pleomorphism within a single species.

Much has been made of the staining reactions of the rickettsia as a character that permits a segregation from bacteria. Many rickettsiae stain less intensely than the majority of bacteria, and their outlines are not as sharp. Some stain well only when Giemsa's method is applied. All the described rickettsiae are gram-negative, and most of them are nonacid-fast. How much one can rely on tinctorial reactions in order to separate one group of micro-organisms from another is difficult to say. I should like to offer the suggestion that in the case of the smaller rickettsiae, the delicacy with which they stain, in contrast with most bacteria, is possibly only apparent rather than real due to the difference in size. A small stained body is likely to be a less effective light screen than a larger one. Some bacterial groups are gram-negative; some gram-positive. The characterization of the group as gram-negative has also exceptions in the rickettsiae (bacteroids, symbionts) of the roaches (*Blattidae*).

The rickettsiae are usually considered nonmotile micro-organisms. However, Buchner (1922) and Hertig and Wolbach (1924) found the filamentous forms in the bedbug definitely motile after Arkwright, Atkin and Bacot (1921) had stated that no motile forms existed. I have examined a number of bedbugs recently, and am convinced that the filaments in the malpighian tubes and in the mycetome are motile.

The rickettsiae within the arthropod host may be extracellular or intracellular and in one case were also intranuclear. They often occur in groups within or on the surface of cells and form masses, producing what has been called the typical picture of "rickettsiae." Some rickettsiae are widely distributed throughout the host; others are restricted to certain tissues. In the ticks infected with Rocky Mountain spotted fever, the micro-organism has intranuclear, intracytoplasmic and extracellular phases, but multiplication occurs only while it is intracytoplasmic and intranuclear. Sometimes, the parasite appears to be restrained, but it may occur within all parts of the alimentary canal, ducts of the salivary glands, all parts of the reproductive system in both sexes, the brain and nerve trunks and the muscles. In short, nearly all the tissues of the tick may become infected with *Dermacentroxenus rickettsi.*

All bedbugs throughout the world are infected with the nonpathogenic *Rickettsia lectularia,* which is present within a mycetome, but according to various writers is also found within the intestine, malpighian tubes, organ of Berlese, ovaries and testes. It has also been found in the blood and produces a general infection. Multiplication, however, occurs entirely intracellularly.

Rickettsia prowazeki in the infected human louse multiplies within the intestinal epithelial cells, and is restricted to these and to the lumen of the alimentary tract. *Rickettsia ruminantium,* in ticks infected with heart-water disease, behaves in much the same manner. Similar events occur in *Melophagus ovinus,* every specimen taken throughout the world being infected with the nonpathogenic *Rickettsia melophagi. Rickettsia wolhynica* (*R. quintana*), in the infected human louse, is entirely extracellular; it occurs and multiplies in enormous numbers within the intestinal lumen and on the surface of the epithelial cells.

Other cases might be cited, but enough has been said to show that the rickettsiae usually occur and multiply intracellularly, but may also occur and multiply extracellularly.

Systemic or cellular reactions do not often occur in arthropods infected with rickettsiae. Wolbach (1919) found no cellular reaction in the tick against *Dermacentroxenus.* The intranuclear forms completely fill the nucleus, but the host does not appear affected. Arkwright, Atkin and Bacot (1921) found that the rickettsiae of the bedbug multiplied to such an extent within the malpighian tubules that certain cells are distended to more than twice their normal diameter. Cowdry (1925) also found no injury of the tissue in sixteen species of ticks other than mechanical distention of certain cells by the parasites. On the other hand, several observers noticed that *Rickettsia prowazeki* often kills lice by excessive multiplication within the intestinal lumen. In these cases, the parasites are said to interfere with the louse's digestion. Baruikin, Zakharov, Kompaneetz and Baruikina (1927) stated that typhus infection in the louse frequently causes a rupture of the epithelium of the intestinal wall, followed by the death of the insect. This may represent a case of reversion or of incomplete adaptation to the host. In general, however, perfect adaptation exists and no serious injury results, even in cases such as that in the spotted fever tick and the bedbug, in which the invertebrate hosts appear to be overwhelmed with parasites.

The question of complete and incomplete adaptation between parasite and host is further strikingly illustrated in the manner in which various arthropods become infected with rickettsiae. The most perfect adaptation exists in those forms in which transmission through the ovum from generation to generation has been established. This manner of infection occurs in most of the species that have been thoroughly investigated. Cowdry in his studies on ticks found that the rickettsiae of all species studied by him are located within the eggs and are transferred to succeeding generations. The rickettsia of the bedbug was found within the ovaries and eggs by Arkwright, Atkin and Bacot and by Hertig and Wolbach. The latter authors also observed a representative of this group of micro-organisms within the ovaries and eggs of

the mosquito, *Culex pipiens.* Nöller found the ova of *Melophagus ovinus* (sheep ked) infected with *Rickettsia melophagi.* In 1923, this author and Kuchling demonstrated the same parasite within the blood of sheep, so it seems likely that the insect may become infected in two ways. Wolbach found that *Dermacentroxenus rickettsi* is transmitted through the ova of the wood ticks infected with spotted fever. This fact was demonstrated experimentally by inoculating guinea-pigs with emulsions of the eggs. Wolbach also found this rickettsia within spermatozoa, but whether transmission to succeeding generations is effected through the male tick is not known. Ricketts long ago had observed another rodlike form present in large numbers in the ovaries and egg cells of the wood tick. Wolbach also found the same form in all the ticks associated with spotted fever, infected and noninfected. He considered it entirely distinct from the micro-organism associated with the disease and found that it was likewise transmitted through the egg. Noguchi (1926) found this micro-organism in the ovaries and eggs of the spotted fever tick and concluded that it was extremely difficult to differentiate the nonpathogenic rickettsia-like organism from *Dermacentroxenus rickettsi.*

Rickettsia prowazeki, R. wolhynica (*R. quintana*) and *R. ruminantium* represent cases of imperfect adaptation to the arthropod vectors.[8] The first two are not transmitted to succeeding generations of human lice and the last one is also not so transmitted by the tick *Amblyomma hebraeum.* These vectors become infected only when they feed on the blood of diseased subjects. In the case of the heart-water tick, however, Cowdry found another form distinct from *Rickettsia ruminantium,* nonpathogenic and more bacterium-like, which is transmitted to succeeding generations through the eggs.

The work on the transmission of the rickettsiae from generation to generation is still in its beginnings. The embryologic phase of the subject has scarcely been touched and until the ova and oviposited eggs have been sectioned and carefully studied it will remain doubtful whether or not more than one species of parasite is involved. This suggestion is worth considering in those cases in which the parasites reveal themselves as extremely pleomorphic forms. Attempts to obtain cultures would, of course, be preferable to a study of sectional material, but obtaining cultures is more difficult and is less likely, at present, to guarantee immediate results. The literature on the intracellular symbionts found in insects abounds in cases of invasions by one, two or three micro-organisms, which usually segregate during the

8. This imperfection is due either to losses of adaptive characters or to the fact that the rickettsiae are still in the process of adaptation to the invertebrates. I incline to the former view for reasons to be divulged later.

embryologic development of the host, follow separate channels of infection and often settle within specific tissues and organs. It must further be recalled that both Cowdry and Wolbach actually found two types within the hosts investigated by them, and, further, Noguchi (1926) had difficulty in differentiating a pathogenic from a non-pathogenic form within the same host.

The micro-organisms under consideration are usually specific for the host. The same species of rickettsiae rarely inhabits two species of invertebrates. Maver (1911) experimentally transmitted Rocky Mountain spotted fever by using three ticks, namely, *Dermacentor marginatus, Dermacentor variabilis* and *Amblyomma americana,* but whether natural infection ever occurs in any manner other than through the bite of the spotted fever tick is questionable. Fletcher, Lesslar and Lewthwaite (1928), however, showed that *Trombicula deliensis* is the normal mite carrier of the tsutsugamuchi virus in Sumatra and in the Malay States, while *Trombicula akamuchi* transmits the disease in Japan and in Formosa.

On the other hand, more than one parasite frequently infects a single host species, and this often makes a differentiation extremely difficult, if not impossible. The human body louse may harbor *Rickettsia prowazeki* or *Rickettsia wolhynica* (*R. quintana*) and perhaps also *Rickettsia pediculi.* The spotted fever ticks at times harbor *Dermacentroxenus rickettsi* and besides are always infected with *Bacillus rickettsiformis* (Noguchi [1926]). The heart-water ticks may be infected with *Rickettsia ruminantium,* but invariably harbor another form. When a nonpathogenic rickettsia is encountered, it always occurs in every individual of the specific host throughout the world.

The rickettsiae that have been tested for their resistance to physical and chemical agents show nothing characteristic that would distinguish them from bacteria and certain other micro-organisms.

Some of the diseases caused by the rickettsiae have been classified with the filtrable viruses from time to time. However, Olitsky (1917, 1922) found that the typhus fever virus does not pass through Berkefeld candles grades "V" and "N." Ricketts (1907), Spencer and Parker (1924) and Spencer (1925) found that the virus of spotted fever behaves in a similar manner. Strong, nevertheless, in 1918, was able to pass the virus of trench fever through a Chamberland "L" filter when it was maintained at a pressure of 760 mm. of mercury. Knuth and du Toit (1921) classed the infective agent of heart-water disease among the filtrable viruses. Theiler, however, according to Cowdry (1926), believed that this virus would not pass through Berkefeld and Chamberland filters. The filtrates used in the aforementioned experiments were not microscopically examined for rickettsiae, but were tested pathogenically for living virus. No experiments in filtra-

tion have been performed with any of the rickettsiae exclusively parasitic in arachnids and insects. It is possible that some rickettsiae under stated conditions might pass through a certain type of filter.

The artificial cultivation of the rickettsiae has been beset with many difficulties, perhaps primarily because they represent a highly specialized group of parasites, exacting in their requirements. The isolation of any member of this group in pure culture is highly desirable so that an insight into its true taxonomic position and biology may be obtained. Many of the species, apparently nonpathogenic to man and higher animals, are highly specialized and parasitic in the invertebrate host. The culture of any one of these might in an unexpected manner lead to the cultivation of a pathogenic form, which, in turn, might yield a prophylactic vaccine or a curative serum.

Weigl (1920) gave normal lice of the human body (*Pediculus humanus*) intrarectal injections of leukocytes from typhus fever patients and from infected guinea-pigs. By so doing, he obtained a growth of *R. prowazeki* in the intestinal tract of the lice. This result was confirmed by Bacot and Segal (1920) and by Arkwright and Bacot (1923). Wolbach and Schlesinger (1923) found that the virus of typhus fever survived in tissue plasma cultures for a length of time corresponding to the survival of endothelial cells, and that the virus multiplied in these cultures. Transplants to fresh tissue cultures were successful. Coccoid, bacillary and filamentous forms appeared in the cultures, thus exactly duplicating the morphology of *R. prowazeki* as described for lice infected with typhus. In a similar manner, Wolbach, Pinkerton and Schlesinger (1922) and Wolbach and Schlesinger (1923) cultivated *Dermacentroxenus rickettsi.* In this case, a filamentous form appeared in the cultures, in addition to the forms already described for the arachnid and mammalian hosts infected with the virus of Rocky Mountain spotted fever.

Sellards (1923) reported the cultivation of *R. nipponica* on "chocolate" blood agar, but Nagayo's work (1924) threw some doubt on the causal relationship between this micro-organism and the "Japanese flood fever."

Sikora, in 1921, cultivated the nonpathogenic *R. pediculi* from lice of the human body in a unique manner. In order to obtain an overabundance of vigorous multiplying forms, she injected concentrated suspensions of *R. pediculi* into the body cavity of lice with extremely fine glass capillary pipets. Previous to this, however, to overcome the antagonism of the phagocytes, she first filled these by injecting the lice with carmine, dead bacteria or blood cells. Under these conditions, the rickettsiae multiplied vigorously within the body of the lice. When the multiplying rickettsiae were then transferred to human blood agar and maintained for twenty days at a temperature of 37 C., round,

flat, grayish-white colonies, the size of pinheads, began to appear. These colonies clung so tightly to the mediums that they were only removed with difficulty. Such cultures showed tremendous number of rickettsiae with many swollen and dead forms. Better initial growths were obtained when the blood agar was inactivated for one half hour at 57 C. Sikora, however, was unable to obtain further transfers of her cultures.

In 1917, Nöller cultivated a *crithidium* from the middle intestine of the sheep ked, *Melophagus ovinus,* on especially prepared semisolid blood agar plates. The blood used in this medium had previously been inactivated. In these cultures, Nöller also discovered a tiny coccobacillus, which was later found occurring plentifully in the intestine of every sheep ked. Nöller thought that this small micro-organism showed a striking morphologic similarity to *Rickettsia prowazeki,* the supposed cause of typhus fever, and for this reason named it *Rickettsia melophagi.* This tiny micro-organism is a short bipolar rod, which, as stated, occurs free in the intestinal lumen of the sheep ked and also within the intestinal epithelial cells. By taking advantage of differences in susceptibility to temperature between the crithidium and the rickettsia, Nöller was able to separate the two forms. On plates held at 29 C., minute, pinpoint, transparent colonies of the micro-organisms began to appear in from ten to fifteen days and many colonies appeared only after forty days. The maximal diameter of these colonies varied between 0.4 and 0.6 mm. When inoculated plates were held at a temperature of 22 C., they remained sterile.

Jungmann, in 1918, further investigated *Rickettsia melophagi* and found that it was a gram-negative, nonacid-fast and nonmotile form, greatly resembling *R. prowazeki* and *R. wolhynica.* He verified Nöller's experiments in cultivation, and by using Nöller's medium obtained growths on slants, as well as on plates, but more rapidly when sheep blood instead of horse blood had been added. Jungmann, moreover, maintained his cultures for several months by transplanting frequently. Cultures attempted in liquid or on routine laboratory mediums invariably remained sterile. Variations of size and form were common; all gradations from coccoid and ovoid shapes to rods were observed, and chains of three or four units were seen. This writer was unable to find *Rickettsia melophagi* in sheep blood, but Nöller and Kuchling, in 1923, found that the micro-organism existed in the blood of sheep and could there be culturally demonstrated. Jungmann discovered a second method of transmission to the ked by observing that the insect's ova become infected during an early stage. This fact was verified by Hertig and Wolbach in 1924. Jungmann emphasized this fundamental difference between the rickettsia of the sheep ked and *Rickettsia*

prowazeki and *R. wolhynica,* neither of which is transmitted from generation to generation. *Rickettsia melophagi* is a normal and regular inhabitant of the intestine of the sheep ked owing to the establishment of hereditary transmission; *Rickettsia prowazeki* and *R. wolhynica,* as previously stated, gain access to the human louse only with infected human blood during the biting process. Further, the form found in the sheep louse does not appear to be pathogenic in laboratory animals, and lastly it can be cultivated on artificial mediums, a feat not yet accomplished for the two forms pathogenic in man. Hertig and Wolbach also succeeded in cultivating Nöller's sheep ked rickettsia, but were unable to obtain the continuous growth of the colonies during long periods as described by Nöller. The colonies of Hertig and Wolbach remained at a barely visible size. These writers found that *Rickettsia melophagi* in cultures behaves like a bacterium and that the organism under these conditions is slightly longer and more definitely rodlike than when in the sheep ked.

Anigstein (1927) isolated five strains of *Rickettsia melophagi,* which he carefully studied morphologically, culturally and serologically. He showed that certain slight differences exist between the strains, but that they correspond to the forms that are found in vivo within the ked and are all closely related. From his work, Anigstein felt that the rickettsiae should not be classified separately; that, on the contrary, they are closely related to the *Corynebacteria* (diphtheroids). He further stated that the rickettsiae are extremely pleomorphic and easily adaptable, and that the so-called rickettsia type is only one of several appearances.

Noguchi (1926) found that the spotted fever tick *Dermacentor venustus* (andersoni), in some instances, revealed several types of micro-organisms morphologically resembling the inciting agent of spotted fever. This investigator cultivated three species from ticks at room temperature on special mediums, but the most consistently grown was a form that he named *Bacillus rickettsiformis.* He had difficulty in obtaining initial growths, but found that a gradual adaptation occurred and that finally less specialized mediums could be employed. The three micro-organisms proved nonpathogenic for guinea-pigs, rabbits and *Macacus rhesus.* In morphologic features, they resemble the forms found in smears and sections of ticks; yet their presence has no relation to the infectivity of the tick infected with the virus of spotted fever. Immunologically, also, the three types are not related to the virus of spotted fever. The three micro-organisms are pleomorphic under cultural conditions, and Noguchi consequently raised the question whether or not the nonpathogenic minute forms of the rickettsia and the somewhat coarser forms found in the tick are morphologic variants caused by differences in nutrition, oxygen tension, tissue reactions, etc.,

in the different tissues and cells in which the parasites are embedded. Noguchi concluded his work by stating: "At all events the differentiation of the nonpathogenic rickettsia-like organisms from *Dermacentroxenus rickettsi* is extremely difficult."

It can finally be stated that *Rickettsia melophagi* from the sheep ked can be properly adapted to artificial mediums. The experiments of Nöller were amply verified by Jungmann, Hertig and Wolbach and Anigstein. It is also highly probable that Sellards cultivated *Rickettsia nipponica* from mites and that Noguchi grew three rickettsia-like micro-organisms from the tick *Dermacentor venustus*. Probably none of the forms pathogenic in higher animals have been adapted to artificial mediums. The experiments of Weigl and of Wolbach and Schlesinger, however, constitute definite advances.

COMMENT

A comparison of the section on the intracellular "symbionts" with that on the "rickettsiae," will show that many of the problems are identical and others overlap. Mites, ticks and insects are exceedingly old creatures and the intracellular symbionts are, as was shown, well adapted to their hosts. Many rickettsiae are also well adapted to their invertebrates, others are not so well adapted. Some workers believe that the virus of Rocky Mountain spotted fever is in the process of adaptation to the tick. It is generally distributed throughout the body and is transmitted through the egg, but not all ticks of the species are infected. In other words, the association appears rather recent. If this line of reasoning is followed in the case of typhus fever, trench fever and heart-water disease, the association of the former two with the louse and of the latter with the tick is to be considered still more recent, because transmission from generation to generation has as yet not been established at all, and the parasites are entirely restricted to the arthropod intestine and to its epithelial layer. In general, it is safer, however, to regard the association as having originated among the invertebrates in the form of disease, because they are phylogenetically older than the vertebrates. On the basis of this conclusion, it is best to assume that some of the intracellular "symbionts" or "rickettsiae" are in the process of adaptation to the higher animals, in which several of them now produce maladies. *Rickettsia melophagi*, according to this assumption, represents a parasite still perfectly adapted to the sheep ked, that only recently began to invade the blood of sheep, where it at present maintains itself without doing any harm. It is perfectly conceivable that this parasite may follow the course adopted by the typhus and the heart-water parasites, in other words, may gradually lose its still perfect adaptation to the invertebrate host and assume

parasitic tendencies in sheep.[9] Many other "symbionts" or "rickettsiae" found in blood-feeding insects, but not yet found in vertebrates, probably have latent parasitic potentialities. This point of view has analogies elsewhere. Most protozoologists believe that the various forms of the hemosporidia of malaria were anopheline parasites before they became pathogenic in birds and in man.

Summing the matter up in another way, one may state that evidence exists for the assumption that the class of micro-organisms discussed are still in the process of a pronounced evolution, and that certain branches may ultimately culminate in a whole series of new and unsuspected diseases among the higher animals. This assumption may be worth a consideration by those who claim that all new diseases arise through mutations of etiologic agents instead of through apparently slower and more orderly processes.

Although this review could not concern itself with the microscopic phases of the diseases due to the rickettsiae in higher animals, it should be mentioned in conclusion that the parasites do not change their habits much after invasion of the vertebrate hosts. Within these, they are all also primarily intracellular parasites. *Rickettsia ruminantium* probably occurs throughout the body of goats, sheep and cattle, but is prevalent in the renal glomeruli and in the capillaries of the cerebral cortex. It is, however, a typical endothelial parasite, restricted in distribution to the endothelial cells of the smaller blood vessels and portions of them that break off into the blood stream. In Rocky Mountain spotted fever and in typhus fever, a specificity for the endothelium of the peripheral blood vessels also exists. This localization of the pathogenic rickettsiae within the blood system of vertebrates proved ideal for the establishment and maintenance of the arthropod vector relationship.

BIBLIOGRAPHY

THE INTRACELLULAR SYMBIONTS

Balbiani, E. G.: Sur la reproduction et embryogénie des pucerons, Compt. rend. Acad. sc. **62**:1231, 1285 and 1390, 1866.

Sur l'embryogénie de la puce, ibid. **81**:901, 1875.

Berlese, A.: Sopra una nuova specie mucedinea parassita del Ceroplastes Rusci, Redia **3**:8, 1905.

9. I realize that this view is unorthodox. It is usually held that when a parasite invades vertebrates, it either is destroyed or multiplies to such an extent that injury to the host follows. According to this prevalent view, a harmless parasite found maintaining itself in vertebrates indicates a terminal stage in its parasitic activities. However, a gradual loss of characters adaptive to the invertebrate accompanied by a gradual adaptation to the higher animals, terminating in true parasitism, appeals more strongly in these specific cases, after due consideration of various general views on the subject.

Blochmann, F.: Ueber die Richtungskörper bei Insekteneiern, Morphol. Jahrb. **12**:544, 1887.

Ueber das regelmässige Vorkommen von bakterienähnlichen Gebilden in den Geweben und Eiern verschiedener Insekten, Ztschr. f. Biol. **24**:1, 1887.

Ueber das Vorkommen von bakterienähnlichen Gebilden in den Geweben und Eiern verschiedener Insekten, Centralbl. f. Bakteriol. **11**:234, 1892.

Breest, F.: Zur Kenntnis der Symbiontenübertragung bei viviparen Cocciden und bei Psylliden, Arch. f. Protistenk. **34**:263, 1914.

Brues, C. T., and Glaser, R. W.: A Symbiotic Fungus Occurring in the Fat Body of Pulvinaria innumerabilis Rath, Biol. Bull. **40**:299, 1921.

Buchner, P.: Studien an intracellulären Symbioten, Arch. f. Protistenk. **26**:1, 1912.

Neue Beobachtungen an intracellulären Symbionten, Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol., Jan. 31, 1919, p. 54.

Zur Kenntnis der Symbiose niederer planzlicher Organismen mit Pedikuliden, Biol. Centralbl. **39**:535, 1919.

Ueber ein neues symbiontisches Organ der Bettwanze, ibid. **41**:570, 1921.

Tier und Pflanze in intracellulare Symbiose, Berlin, G. Bornträger, 1921.

Rassen- und Bakteroidenbildung bei Hemipterensymbionten, Biol. Centralbl. **42**:38, 1922.

Haemophagie und Symbiose, Die Naturwissenschaften **33**:1, 1922.

Studien an intracellulären Symbionten: IV. Die Bakteriensymbiose der Bettwanze, Arch. f. Protistenk. **46**:225, 1923.

System und Symbiose, Verhandl. d. deutsch. zool. Gesellsch. **29**:48, 1924.

Intracelluläre Symbiose der Tiere mit pflanzlichen Mikroorganismen, in Abderhalden, E.: Handb. d. biol. Arbeitsmeth., Berlin, Urban & Schwarzenberg, 1925, pt. 12. Leistungen der niederen Organismen Welt, sec. 1, p. 325.

Cholodowsky, N.: Die Embryonalentwicklung von Phyllodromia (Blatta germanica), Mém. Acad. St. Pétersbourg **38**:1, 1891.

Conté, A., and Faucheron, L.: Présence de levures dans le corps adipeus de divers coccides, Compt. rend. Acad. sc. **145**:1223, 1907.

Cuénot, L.: Etudes physiologiques sur les orthoptères, Arch. de biol. **14**:293, 1896.

Escherich, K.: Ueber das regelmässige Vorkommen von Sprosspilzen in dem Darmepithel eines Käfers, Biol. Centralbl. **20**:349, 1900.

Florence, L.: An Intracellular Symbiont of the Hog Louse, Am. J. Trop. Med. **4**:397, 1924.

Forbes, S. A.: Bacteria Normal to Digestive Organs of Hemiptera, Bull. Illinois State Lab. Nat. Hist., 1896, vol. 4, art. 1, p. 1.

Henneguy, L.: Les insectes, Paris, Masson & Cie, 1904.

Hertig, M.: Attempts to Cultivate the Bacteroids of the Blattidae, Biol. Bull. **41**:181, 1921.

Hertig, M., and Wolbach, B. S.: Studies on Rickettsia-Like Microorganisms in Insects, J. M. Research **44**:329, 1924.

Huxley, T.: On the Agamic Reproduction and Embryology of Aphids, Tr. Linn. Soc. London **22**:193, 1858.

Javelly, E.: Les corps bactéroides de la blatte (Periplaneta orientalis) n'ont pas encore été cultivées, Compt. rend. Soc. de biol. **77**:413, 1914.

Klevenhusen, F.: Beiträge zur Kenntnis der Aphidensymbiose, Ztschr. f. wissensch. Biol., sec. A, Morphol. u. Ökol. Tiere **9**:97, 1927.

Krassilschtschik, M.: Sur les bactéries biophytes; note sur la symbiose des pucerons avec les bactéries, Ann. de l'Inst. Pasteur **3**:465, 1889.

Ueber eine Kategorie von Bacterien (Biophyten) die im Innern eines Organismus leben und ihm Nützen bringen, 8th Kongress Russ. Naturf. Arzte. Sitz., Jan. 16, 1890; abstr., Biol. Centralbl. **10**:421, 1890.

Leydig, F.: Einige Bemerkungen über die Entwicklung der Blattläuse, Ztschr. f. wissensch. Zool. **2**:62, 1850.

Zur Anatomie von Coccus hesperidum, ibid. **5**:1, 1854.

Lindner, P.: Ueber eine in Aspidiotus nerii parasitischlebende Apiculatus-Hefe, Centralbl. f. Bakteriol. **1**:782, 1895.

Lwoff, A.: Nature et position systématique du bactéroide des blattes, Compt. rend. Soc. de biol. **89**:945, 1923.

Mercier, L.: Les corps bactérioides de la blatte (Periplaneta orientalis) Bacillus Cuenoti (n. sp. L. Mercier), Compt. rend. Soc. de biol. **61**:682, 1906.

Recherches sur les bactéroides des blattides, Arch. f. Protistenk. **9**:346, 1907.

Cellules à Bacillus Cuenoti dans la paroi des gaines ovariques de la blatte, Compt. rend. Soc. de biol. **62**:758, 1907.

Metschnikoff, E.: Untersuchungen über die Embryologie der Hemipteren, Ztschr. f. wissensch. Zool. **16**:128, 1866.

Embryologische Studien an Insecten, ibid. **16**:389, 1866.

Meyer, K. F.: The "Bacterial Symbiosis" in the Concretion Deposits of Certain Operculate Land Mollusks of the Families Cyclostomatidae and Annulariidae, J. Infect. Dis. **36**:1, 1925.

Milovidov, P. F.: A propos des bactéroides des blattes (Blattella germanica), Compt. rend. Soc. de biol. **99**:127, 1928.

Moniez, R.: Sur une champignon parasite du Lecanium hesperidorum (Lecaniascus polymorphus nobis), Bull. Soc. de zool. **12**:150, 1887.

Neukomm, A.: Sur la structure des bactéroides des blattes, (Blattela germanica), Compt. rend. Soc. de biol. **96**:306, 1927.

Action des rayons ultra-violets sur bactéroides des blattes (Blattela germanica), ibid. **96**:1155, 1927.

Nuttall, G. H. F.: Symbiosis in Animals and Plants, Am. Naturalist **57**:449, 1923.

Peklo, J.: Ueber symbiontische Bakterien der Aphiden, Ber. d. deutsch. bot. Gesellsch. **30**:416, 1912.

Ueber die Blutlaus (tschechisch), Landwirtschaft. Arch. (Zcmedelskéko Archion), 1916, vol. 7.

Petri, L.: Sopra la particolare localizzazione di una colonia batterica nel tubo digerente della larva della Mosca olearia, Atti d. r. Accad. Lincei. 13, ser. 5, 1904, pp. 482 and 560.

Pierantoni, U.: L'origine di alcuni organi d'Icerya purchasi e la simbiosi ereditaria, Boll. d. Soc. di nat. in Napoli **23**:147, 1909.

Ulteriori osservazioni sulla simbiosi ereditaria degli Omotteri, Zool. Anz. **36**:96, 1910.

Osservazioni su Aphrophora spumaria, Boll. d. Soc. di Nat. in Napoli, 1910, vol. 24.

La simbiosi ereditaria e la biologia sessuale d'Icerya, Monitore. zool. ital. **21**: 294, 1910.

Sul corpo ovale del Dactylopius, Boll. d. Soc. di Nat. in Napoli **24**:303, 1911.

Origine e struttura del corpo ovale del Dactylopius citri, etc., ibid. **24**:1, 1911.

Struttura ed evoluzione dell' organo simbiotico di Pseudococcus citri Risso, etc., Arch. f. Protistenk. **31**:300, 1913.

La luce degli insetti luminosi e la simbiosi ereditaria, R. C. Acad. d. sc. fis. math., Napoli, 1914, vol. 1, p. 15.

Porta, A.: Ricerche sulla Aphrophora spumaria L., Rendic. Int. Lomb. Sc. Lett. **33**:920, 1900.

La secrezione della spuma nella Aphrophora, Monitore. zool. ital. **12**:57, 1901.

Reichenow, E.: Ueber intracelluläre Symbionten bei Blut Saugern, Arch. Schiffs- u. Tropen-Hyg. **25**:366, 1921.

Intracelluläre Symbionten bei blutsaugenden Milben und Egeln, Arch. f. Protistenk. **45**:95, 1922.

Roubaud, E.: Les particularités de la nutrition et la vie symbiotique chez les mouches tsétsés, Ann. de l'Inst. Pasteur **33**:489, 1919.

Schaudinn, F.: Generations und Wirtswechsel bei Trypanosoma und Spirochäte, Arb. a. d. kais. Gesndhsamte **20**:387, 1904.

Schrader, F.: A Study of the Chromosomes in Three Species of Pseudococcus, Arch. f. Zellforsch. **17**:45, 1923.

The Origin of the Mycetocytes in Pseudococcus, Biol. Bull. **45**:279, 1923.

Schrader, F., and Hughes-Schrader, S.: Haploidy in Icerya purchasi, Ztschr. f. wissensch. Zool. **128**:182, 1926.

Schrader, S. H.: Origin and Differentiation of the Male and Female Germ Cells in the Hermaphrodite of Icerya purchasi (Coccidae), Ztschr. f. Zellforsch. u. mikr. Anat. **6**:509, 1927.

Schwartz, W.: Untersuchungen über die Pilzsymbiose der Schildlause, Biol. Centralbl. **44**:487, 1924.

Shinji, G. O.: Embryology of Coccids, with Special Reference to the Formation of the Ovary, Origin and Differentiation of the Germ Cells, Germ Layers, Rudiments of the Mid-Gut and the Intracellular Symbiotic Organisms, J. Morphol. **33**:73, 1919.

Sikora, H.: Vorläufige Mitteilung über Mycetome bei Pediculiden, Biol. Centralbl. **39**:287, 1919.

Stuhlmann, F.: Beiträge zur Kenntnis der Tsetsefliege, Arb. a. d. kais. Gesndhtsamte **26**:301, 1907.

Sülç, K.: Kermincola kermesina n. g., n. sp. und Physokermina n. sp., neue Mikro-endosymbiontiker der Cocciden, Sitzungsb. d. k.-böhm. Gesellsch. d. Wissensch., Prag., 1906, art. 19.

"Pseudovitellus" und ähnliche Gewebe der Homopteren sind Wohnstätten symbiotischer Saccharomyceten, ibid. 1910, art. 3.

Symbiotische Saccharomyceten der echten Cicaden (Cicadidae), ibid., 1910.

Teodoro, G.: Richerche sull' emolinfa dei lecanini, Atti Acad. ven-trent.-istr., **5**:72, 1912.

Osservazione sulla ecologia delle cocciniglie con speciale riguardo alla morfologia e alla fisiologia de questi insetti, Redia **11**:129, 1916.

Alcune osservazioni sui saccaromiceti del Lecaninus persicae Fab., ibid. **13**:1, 1918.

Uichanco, L. P.: Studies on the Embryogeny and Postnatal Development of the Aphididae with Special Reference to the History of the "Symbiotic Organ," or "Mycetom," Philippine J. Sc. **24**:143, 1924.

Wheeler, W. M.: The Embryology of Blatta germanica and Doryphora decimlineata, J. Morphol. **3**:291, 1889.

A Contribution to Insect Embryology, ibid. **8**:1, 1893.

THE RICKETTSIAE

Anigstein, L.: Untersuchungen über die Morphologie und Biologie der Rickettsia melophagi Nöller, Arch. f. Protistenk. **57**:209, 1927.

Arkwright, J. A.: Rickettsia (Laboratory Demonstration), Tr. Roy. Soc. Trop. Med. & Hyg. **17**:3, 1923.

The Position of Rickettsia as an Aetiological Factor in Disease, J. Roy. Army M. Corps **42**:447, 1924.

Arkwright, J. A.; Atkin, E. E., and Bacot, A.: An Hereditary Rickettsia-Like Parasite of the Bedbug (Cimex lectularius), Parasitology **13**:27, 1921-1922.

Arkwright, J. A., and Bacot, A.: Stages of Rickettsia in the Sheep Ked, Melophagus ovinus, Tr. Roy. Soc. Trop. Med. & Hyg. **15**:146, 1921.

Observations on the Morphology of Rickettsia prowazeki Occurring in Lice (Pediculus humanus) Infected with the Virus of Typhus Fever, Parasitology **15**:43, 1923-1924.

Investigation of the Aetiology of Typhus Fever, Brit. J. Exper Path. **4**:70, 1923.

Arkwright, J. A.; Bacot, A., and Duncan, F. M.: The Minute Bodies (Rickettsia) Found in Association with Trench Fever, Typhus Fever and Rocky Mountain Spotted Fever, Tr. Roy. Soc. Trop. Med. & Hyg. **12**:61, 1919.

The Association of Rickettsia with Trench Fever, J. Hyg. **18**:76, 1919.

Atkin, E. E., and Bacot, A.: Experiments on the Infectivity of Typhus Virus, Brit. J. Exper. Path. **3**:196, 1922-1923.

Bacot, A.: On the Probable Identity of Rickettsia pediculi with Rickettsia quintana, Brit. M. J. **1**:156, 1921.

Details of the Technique Adopted in Following Weigl's Plan of Feeding Lice Infected with the Virus of Typhus Fever by Rectal Injection, Brit. J. Exper. Path. **3**:72, 1922

Bacot, A., and Segal, J.: The Infection of Lice (Pediculus humanus) with Rickettsia prowazeki by the Injection Per Rectum of the Blood Platelets of Typhus-Infected Guinea-Pigs and the Reinfection of Other Guinea-Pigs with These Lice, Brit. J. Exper. Path. **3**:125, 1922-1923.

Baruikin, V.; Zakharov, A.; Kompaneetz, A., and Baruikina, O.: Observations on Typhus Fever: II. Typhus Fever in Clothes Lice (in Russian with a Summary in French), Zh. eksperim, Biol. Med. **8**:2, 1927.

Bruce, D.: Trench Fever: Final Report of the War Office Trench Fever Investigation Committee, J. Hyg. **20**:258, 1921-1922.

Brumpt, E.: Au sujet d'un parasite (Rickettsia prowazeki) des poux de l'homme considéré, à tort, comme l'agent causal du typhus exanthématique, Bull. Soc. path. exot. **11**:249, 1918.

Cowdry, E. V.: The Distribution of Rickettsia in the Tissues of Insects and Arachnids, J. Exper. Med. **37**:431, 1923.

A Group of Microorganisms Transmitted Hereditarily in Ticks and Apparently Unassociated with Disease, J. Exper. Med. **41**:817, 1925.

The Occurrence of Rickettsia-Like Microorganisms in Adult "Locusts" (Tibicen septendecim Linn.), Biol. Bull. **48**:15, 1925.

Studies on the Etiology of Heartwater: I. Observation of a Rickettsia, Rickettsia ruminantium (n. sp.) in the Tissues of Infected Animals, J. Exper. Med. **42**:231, 1925; II. Rickettsia ruminantium (n. sp.) in the Tissues of Ticks Transmitting the Disease, ibid. **42**:253, 1925.

Rickettsiae and Disease, Arch. Path. **2**:59 (July) 1926.

Epstein, H.: Beiträge zur Kenntnis der Ricksettsia prowazeki, Centralbl. f. Bakteriol. **87**:553, 1922.

Fletcher, W.; Lesslar, J. E., and Lewthwaite, R.: The Aetiology of the Tsutsugamushi Disease and Tropical Typhus in the Federated Malay States, Tr. Roy. Soc. Trop. Med. & Hyg. **22**:161, 1928.

Guimarais, A.: Flore microbienne du Phthirius inguinalis; remarque sur des éléments de nature rickettsienne, Compt. rend. Soc. de biol. **87**:711, 1922.

Hegler, C., and von Prowazek, s.: Untersuchungen über Fleckfieber (vorlaüfiger Bericht), Berl. klin. Wchnschr. **50**:2035, 1913.

Hertig, M., and Wolbach, B. S.: Studies on Rickettsia-Like Microorganisms in Insects, J. M. Research **44**:100, 1924.

Hindle, E.: Notes on Rickettsia, Parasitology **13**:152, 1921.

Jungmann, P.: Zur Aetiologie des "Febris Wolhynica," Berl. klin. Wchnschr. **53**:323, 1916.

Untersuchungen über Schaflausrickettsien (Rickettsia melophagi Nöller), Deutsche med. Wchnschr. **49**:1346, 1918.

Das Wolhynische Fieber, Berlin, Julius Springer, 1919.

Jungmann, P., and Kuczynski, M. H.: Zur Klinik und Aetiologie de Febris Wolhynica, Deutsche med. Wchnschr. **43**:359, 1917.

Kawamura, R., and Yamaguchi, M.: Ueber die Tsutsugamushi Krankheit in Formosa, Kitasato Arch. Exper. Med. **4**:169, 1921.

Kligler, I. J., and Ashner, M.: Studies on the Etiology of Phlebotomus and Dengue Fever: II. Is a Leptospira the Causative Virus? Ann. Trop. Med. **22**:151, 1928.

Knuth, P., and du Toit, P. J.: Tropenkrankheiten der Haustiere, in Mense, C.: Handbuch der Tropenkrankheiten, Leipzig, Barth, 1921.

Lewthwaite, R.: Japanese River Fever, Malayan M. J. **2**:145, 1927.

Maver, M. B.: Transmission of Spotted Fever by Other Than Montana and Idaho Ticks, J. Infect. Dis. **8**:322, 1911.

Megaw, J. W. D., and Rao, S. S.: Tick-Typhus and Other Sporadic Fevers of the Typhus Group, Ind. M. Gaz. **63**:306, 1928.

Munk, F., and da Rocha-Lima, H.: Klinik und Aetiologie des sogenannten "Wolhynischen Fiebers": II. Ergebnis der aetiologischen Untersuchungen und deren Beziehungen zur Fleckfieberforschung, München. med. Wchnschr. **44**:1422, 1917.

Nagayo, M.; Tamiya, T.; Imamura, A.; Sato, K.; Miyagawa, Y., and Mitamura, F.: Demonstration of the Virus of Tsutsugamushi Disease, Sc. Rep. Gov. Inst. Infect. Dis., Tokyo **3**:37, 1924.

Noguchi, H.: Cultivation of Rickettsia-Like Microörganisms from the Rocky Mountain Spotted Fever Tick, Dermacentor andersoni, J. Exper. Med. **43**: 515, 1926.

Nöller, W.: Beiträg zur Flecktyphusübertragung durch Lause, Berl. klin. Wchnschr. **53**:778, 1916.

Blut- und Insektenflagellaten Züchtung auf Platten, Arch. f. Schiffs- u. Troper.-Hyg. **21**:53, 1917.

Neue Züchtungserbegnisse bei Blut- und Insekten Parasiten, Berl. klin. Wchnschr. **54**:346, 1917.

Nöller, W., and Kuchling, M.: Zur Züchtung des Schaftrypanosomas und der Schaflausrickettsia aus dem Schafblute, Centralbl. f. Bakteriol **75**:237, 1923.

Olitsky, P. K.: The Nonfiltrability of Typhus-Fever Virus, J. Infect. Dis. **20**:349, 1917.

Otto, R.: Zur Kultur der Rickettsia prowazeki, Klin. Wchnschr. **1**:1746, 1922.

Parker, R. R.: Some Results of Two Years' Investigation of the Rocky Mountain Spotted Fever Tick in Eastern Montana, J. Econom. Entomol. **11**:159, 1918.

Second Report on Investigations of the Rocky Mountain Spotted Fever Tick in Eastern Montana, Third Biennial Report Montana State Board of Entomolgy, 1919, p. 41.

Transmission of Rocky Mountain Spotted Fever by the Rabbit Tick, Heamaphysalis leporispalustris Packard, Am. J. Trop. Med. **3**:39, 1923.

Von Prowazek, S.: Aetiologische Untersuchungen über den Flecktyphus in Serbien 1913 and Hamburg 1914, Beitr. z. Klin. d. Infektionskrankh. u. z. Immunitätsforsch. **4**:5, 1915.

Ricketts, H. T.: Observations on the Virus and Means of Transmission of Rocky Mountain Spotted Fever, J. Infect. Dis. **4**:141, 1907.

A Microorganism Which Apparently Has a Specific Relationship to Rocky Mountain Spotted Fever, J. A. M. A. **52**:379 (Jan. 30) 1909.

Ricketts, H. T., and Wilder, R. M.: The Transmission of the Typhus Fever of Mexico (Tabardillo) by Means of the Louse (Pediculus vestimenti), J. A. M. A. **54**:1304 (April 16) 1910.

Da Rocha-Lima, H.: Beobachtungen bei Flecktyphusläusen, Arch. f. Schiffs- u. Troper.-Hyg. **21**:17, 1916.

Zur Aetiologie des Fleckfiebers, Deutsche med. Wchnschr. **42**:1353, 1916.

Zum Nachweis der Rickettsia prowazeki bei Fleckfieberkranken, München. med. Wchnschr. **64**:33, 1917.

Die Uebertragung des Rückfallfiebers und des Fleckfiebers, Deutsche med. Wchnschr. **45**:732, 1919.

Die Aetiologie des Fleckfiebers, Ergebn. d. allg. Path. u. path. Anat. **19**:159, 1919.

Rosenberger, G.: Studien über die in- und extracellulär liegenden Rickettsien, Arch. f. Schiffs- u. Troper.-Hyg. **26**:112, 1922.

Sambon, L. W.: The Parasitic Acrians of Animals and the Part They Play in the Causation of the Eruptive Fevers and Other Diseases of Man. Preliminary Considerations Based upon an Ecological Study of Typhus Fever, Ann. Trop. Med. **22**:67, 1928.

Sellards, A. W.: The Cultivation of a Rickettsia-Like Microörganism from Tsutsugamushi Disease, Am. J. Trop. Med. **3**:529, 1923.

Sellards, A. W., and Siler, J. F.: The Occurrence of Rickettsia in Mosquitoes (Aëdes aegypti) Infected with the Virus of Dengue Fever, Am. J. Trop. Med. **8**:299, 1928.

Sikora, H.: Beiträge zur Kenntnis der Rickettsien, Arch. f. Schiffs- u. Troper.-Hyg. **22**:144, 1918.

Boabachtung an Rickettsien, besonders zur Unterscheidung der R. prowazeki von R. pediculi, ibid. **24**:347, 1920.

Ueber die Züchtung der Rickettsia pediculi, ibid. **25**:123, 1921.

Neue Rickettsia bei Vogelläusen, ibid. **26**:271, 1922.

Der gegenwärtige Stand der Rickettsiaforschung, Klin. Wchnschr. **3**:2008, 1924.

Rickettsienfund bei einer staupeartigen Krankheit der Katze, Berl. tierärztl. Wchnschr. **40**:531, 1924.

Siler, J. F.; Hall, M. W., and Hitchens, A. P.: Dengue, Manila, P. I., Bur. Science, 1926.

De Sousa, J.: Presence de Rickettsia prowazeki dans le sang des convalescents de typhus exanthématique, Compt. rend. Soc. de biol. **87**:710, 1922.

Spencer, R. R.: Rocky Mountain Spotted Fever: Non-Filterability of Tick and Blood Virus, Washington, D. C., Government Printing Office, 1925.

Spencer, R. R., and Parker, R. R.: Rocky Mountain Spotted Fever: Infectivity of Fasting and Recently Fed Ticks, Pub. Health Rep. **38**:333, 1923; Viability of the Virus in Animal Tissues, ibid. **39**:55, 1924; Experimental Studies on Tick Virus, ibid. **39**:3027, 1924; Non-Filterability of Tick and Blood Virus, ibid. **39**:3251, 1924.

Strong, R. P.: American Red Cross Medical Research Committee, Report of Commission on Trench Fever, New York, Oxford University Press, 1918.

The Significance of Rickettsia in Relation to Disease, Tr. A. Am. Phys. **34**:322, 1919.

Swift, H. F.: Trench Fever, Arch. Int. Med. **26**:76 (July) 1920.

Töpfer, H.: Zur Aetiologie des "Febris wolhynica," Berl. klin. Wchnschr. **53**:323, 1916.

Der Fleckfiebererreger in der Laus, Deutsche med. Wchnschr. **42**:1251, 1916.

Zur Ursache und Uebertragung des Wolhynischen Fiebers, München. med. Wchnschr. **63**:1495, 1916.

Töpfer, H., and Schüssler, H.: Zur Aetiologie des Fleckfiebers, Deutsche med. Wchnschr. **42**:1157, 1916.

Weigl, R.: Studies on Rickettsia prowazeki, Przeglad. Epidemjologiczny **1**:15, 1920.

Further Studies on Rickettsia rocha-limae (n. sp.), ibid. **1**:375, 1921.

Die Beziehungen der X Stämme zur Rickettsia prowazeki, Ztschr. f. Hyg. u. Infektionsrkankh. **99**:303, 1923.

Der gegenwärtige Stand der Rickettsiaforschung, Klin. Wchnschr. **3**:1590 and 1636, 1924.

Further Studies on Rickettsia rocha-limae (n. sp.), J. Trop. Med. **27**:14, 1924.

Wolbach, S. B.: Studies on Rocky Mountain Spotted Fever, J. M. Research **41**:1, 1919.

Rickettsiae and Their Relationship to Disease, J. A. M. A. **84**:723 (March 7) 1925.

Wolbach, S. B.; Pinkerton, H., and Schlesinger, M. J.: The Cultivation of the Organisms of Rocky Mountain Spotted Fever and Typhus in Tissue Cultures, Proc. Soc. Exper. Biol. & Med. **20**:270, 1922.

Wolbach, S. B., and Schlesinger, M. J.: The Cultivation of Microorganisms of Rocky Mountain Spotted Fever (Demacentroxenus rickettsi) and of Typhus Rickettsia prowazeki) in Tissue Plasma Cultures, J. M. Research **44**:231, 1923.

Wolbach, S. B.; Todd, J. L., and Palfrey, F. W.: The Etiology and Pathology of Typhus, Cambridge, Mass., Harvard University Press, 1922.

Woodcock, H. M.: "Rickettsia" Bodies as a Result of Cell Digestion or Lysis, J. Roy. Army M. Corps **40**:81 and 241, 1923.

The Rickettsia Question, Klin. Wchnschr. **4**:266, 1925.

OTHER WORKS CONSULTED

Baumberger, J. P.: A Nutritional Study of Insects with Special Reference to Microorganisms and Their Substrata, J. Exper. Zool. **28**:1, 1919.

Berlese, A.: Gli Insetti, Milan, Società Editrice, Libraria, 1909.

Cleveland, L. R.: The Physiological and Symbiotic Relationships Between the Intestinal Protozoa of Termites and Their Host, with Special Reference to Reticulitermes flavipes Kollar, Biol. Bull. **46**:177, 1924.

The Effects of Oxygenation and Starvation on the Symbiosis Between the Termite, Termopsis, and Its Intestinal Flagellates, ibid. **48**:309, 1925.

The Method by Which Trichonympha campanula, a Protozoon in the Intestine of Termites, Ingests Solid Particles of Wood for Food, ibid. **48**:282, 1925.

Cowdry, E. V., and Olitsky, P. K.: Differences Between Mitochondria and Bacteria, J. Exper. Med. **36**:521, 1922.

Dahlgren, U.: A Combination of the Paraffin and Celloidin Methods of Imbedding, J. Applied Microscopy **1**:67, 1898.

Glaser, R. W.: The Relation of Microorganisms to the Development and Longevity of Flies, Am. J. Trop. M. **4**:85, 1924.

Glasgow, H.: The Gastric Caeca and the Caecal Bacteria of the Heteroptera, Biol. Bull. **26**:101, 1914.

Guillermond, A.: Mitochondries et symbiotes, Compt. rend. Soc. de biol. **82**:309, 1919.

Guyénot, E.: Etudes biologiques sur une mouche Drosophila ampelophila Loew: I. Possibilité de vie aseptique pour l'individu et la lingee, Compt. rend. Soc. de biol. **74**:97, 1913; II. Rôle de levures dans l'alimentation, ibid. **74**:178, 1913.

Hertwig, O.: Die Symbiose im Tierreich, Jena, 1883.

Hertwig, R.: Manual of Zoology, translated by J. S. Kingsley, New York, Henry Holt & Company, 1912.

Imms, A. D.: A General Textbook of Entomology, New York, E. P. Dutton & Company, 1924.

Korschelt, E., and Heider, K.: Lehrbuch der vergleichenden Entwicklungsgeschichte der wirbellosen Thiere, Jena, 1892, no. 2; translated by Bernard, M., and Woodward, M. F.: Textbook of the Embryology of Invertebrates, New York, The Macmillan Company, 1899.

Loeb, J., and Northrop, J. H.: Nutrition and Evolution, J. Biol. Chem. **27**:309, 1916.

Lumière, A.: Le Mythe des symbiotes, Paris, Masson & Cie, 1919.

Macfie, J. W. S.: Observations on the Rôle of the Cockroaches in Disease, Ann. Trop. Med. & Parasitol. **16**:441, 1922-1923.

Miall, L. C., and Denny, A.: The Cockroach, London, Lovell Reeve & Company, 1886.

Northrop, J. H.: The Rôle of Yeast in the Nutrition of an Insect (Drosophila), J. Biol. Chem. **30**:181, 1917.

Nuttall, G. H. F.: The Part Played by Pediculus humanus in the Causation of Disease, Parasitology **10**:43, 1917.

Portier, P.: Les symbiotes, Paris, Masson & Cie, 1918.

Regaud, C.: Mitochondries et symbiotes, Compt. rend. Soc. de biol. **82**:244, 1919.

Schuchert, Charles: A Textbook of Geology: Historical Geology, New York, John Wiley & Sons, 1924.

Strong, R. P.: The Relationship of Certain "Free-Living" and Saprophytic Microorganisms to Disease, Science **61**:97, 1925.

Trojan, E.: Bekteroiden, Mitochondrien und Chromidien, Ein Beiträg zur Entwicklung des Bindegewebes, Arch. f. mik. Anat. **93**:333, 1919-1920.

Wallin, I. E.: On the Nature of Mitochondria, Am. J. Anat. **30**:203 and 451, 1922. Observations on Mitochondrial Growth in Artificial Culture Media, Proc. Soc. Exper. Biol. & Med. **25**:371, 1928.

Wheeler, W. M.: Social Life Among the Insects, New York, Harcourt, Brace & Company, 1923.

Wollman, E.: Sur l'élevage des mouches stériles: Contribution à la connaissance du rôle des microbes dans les voies digestive, Ann. de l'inst. Pasteur **25**:78, 1911.

Elevage aseptique de larves de la mouche à viande (Calliphora vomitoria) sur milieu sterilisé à haute température, Compt. rend. Soc. de biol. **82**:593, 1919.

Larves de mouche (Calliphora vomitoria) et vitamines, Compt. rend. Soc. de biol. **82**:1208, 1919.

Biologie de la mouche domestique et des larves de mouches à viande, an élevage aseptiques, Ann. de l'inst. Pasteur **36**:784, 1922.

Notes and News

University News, Appointments, Promotions, Resignations.—On his retirement from the professorship of pathology and bacteriology in Tufts College Medical School, Boston, Timothy Leary was honored at a complimentary dinner.

Max Cutler has assumed charge of the New York City Cancer Institute.

Everett S. Sanderson is now in charge of the department of pathology and bacteriology in the school of medicine of the University of Mississippi.

Edmund V. Cowdry, professor of cytology, Washington University, St. Louis, will study parasitic diseases in East Africa at the request of the British government.

Theobald Smith and James Ewing have accepted appointments as consultant in bacteriology and in pathology, respectively, to the division of laboratories and research of the State Department of Health at Albany, New York.

In Berlin, B. Fraenckel has been placed in charge of the medicolegal institute, pending selection of a permanent successor to F. Strassmann, the former director.

Jefferson H. Clark has been appointed director of the laboratory of the Philadelphia General Hospital.

Barton W. Johnson has been appointed pathologist and radiologist at the General Hospital, Mansfield, Ohio, to take the place of Samuel H. Richman, who has accepted a like position in the Sherman Hospital, Elgin, Ill.

Kenneth Goodner has been appointed instructor in bacteriology and immunology in the school of public health at Harvard University.

Henry H. Plowden has been appointed director of the pathologic laboratory of the Columbia Hospital, Columbia, S. C.

In the school of medicine of the University of Illinois, Lloyd Arnold has been made professor of bacteriology and preventive medicine; I. Pilot, associate professor of pathology and medicine, and R. J. Kremer, instructor in pathology and bacteriology.

Ella Sachs Plotz Foundation.—During the past year, twenty-four grants were made, most of them to investigators outside of the United States. The amounts granted varied from $250 to $1,000. Seven of the investigations aided relate to the general topic of nephritis. During the six years of its existence, the Foundation has made ninety-five grants. Applications for grants for 1930-1931 must be made before May 1, 1930. Address Dr. Joseph C. Aub, 695 Huntington Avenue, Boston.

Grant for Study of Trachoma.—The Commonwealth Fund of New York has made a grant of $50,000 toward the investigation, during a period of five years, of trachoma and other infectious diseases of the eye at the Department of Ophthalmology of the Washington University School of Medicine.

Grant for Study of Undulant Fever.—The Commonwealth Fund of New York has made a grant of $18,800 to the National Research Council in Washington, D. C., toward a three year program of research on problems of undulant fever at the Central Brucella Station, Michigan State College, East Lansing, Mich., under the auspices of the Council's committee on infectious abortion.

Philadelphia Pathological Society.—The recently elected officers of the society are Baldwin Lucke, president; V. H. Moon, vice-president, and Isolde T. Zeckwer, secretary-treasurer.

British Medical Association.—At the annual meeting of the association in Winnipeg, Canada, Aug. 25-29, 1930, there will be a joint section on pathology, bacteriology, physiology and biochemistry, of which Robert Muir will be the president and G. Hadfield (Royal Free Hospital, Gray's Inn Road, W. C. 1, London) the secretary.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

STUDIES ON SEX (INTERSTITIAL CELLS IN GIGANTISM). WILLIAM G. DOWNS, JR., Am. J. Path. **5**:295, 1929.

The case presented here, a definite giant, did not have the hypoplastic genitalia or the marked feminine secondary sex characteristics usually associated with such a condition. Microscopically there was an apparently complete absence of testicular interstitial cells, which, while they are supposed to limit bone growth, are likewise supposed to produce, in part at least, the masculine type of secondary sex characteristics.

AUTHOR'S SUMMARY.

THE EFFECT OF POTASSIUM IODIDE, THYROID EXTRACT AND ANTERIOR PITUITARY EXTRACT UPON REGENERATION AND EARLY COMPENSATORY HYPERTROPHY OF THE THYROID GLAND. S. H. GRAY, Am. J. Path. **5**:415, 1929.

Regeneration of thyroid tissue after an incision occurs rapidly in control and potassium iodide-fed animals. Regeneration is delayed by the feeding of pituitary extract and thyroid extract. Early compensatory hypertrophy is markedly inhibited by pituitary extract and thyroid extract but only slightly by potassium iodide. The possible causes of a slight diminution in the average hypertrophy in the potassium iodide series which was observed at early periods are discussed. Compensatory hypertrophy may appear as early as eight days following the removal of parts of the thyroid gland.

AUTHOR'S SUMMARY.

AUTOTRANSPLANTATION AND HOMOIOTRANSPLANTATION OF CROSS-STRIATED MUSCLE TISSUE IN THE RAT. JULIUS ELSON, Am. J. Path. **5**:425, 1929.

After autotransplantation of striated muscle tissue in the rat, well preserved muscle tissue was found as late as 118 days after transplantation; the further fate of the muscle tissue has not yet been studied. After homoiotransplantation there is less regeneration of the muscle tissue in the first period after transplantation, and much more degeneration due to invasion by lymphocytes and, to a less extent, by connective tissue at subsequent periods. As a result of these conditions, homoiotransplanted muscle disappears much earlier than autotransplanted muscle, no preserved tissue being present at fifty days. It is therefore probable that in addition to the action of the lymphocytes, the homoiotoxins may injure the muscle tissue directly, diminishing the regenerative process and increasing the subsequent degeneration. Nowhere is there seen a true outgrowth of muscle fibers, either in continuity with the preformed transplanted muscle or by budding. The old muscle tissue, after a primary degeneration of its major portion, undergoes regenerative processes, consisting in an increase of its sarcoplasm and a proliferation of its nuclei; subsequently there is a differentiation of the sarcoplasm into typical striated muscle, in which cross-striations are again formed. In the course of time the nuclear proliferation becomes less active; the nuclei decrease in number and become situated peripherally within the fibers, while the fibers as such increase in size until there are almost normal muscle fibers. This process of growth is, in certain respects, comparable to compensatory hypertrophy or hyperplasia rather than to regeneration in the strict sense.

AUTHOR'S SUMMARY.

VASODEPRESSOR SUBSTANCES IN THE LIVER AFTER OBSTRUCTION OF THE COMMON DUCT. I. S. RAVDIN, Arch. Surg. **18**:2191, 1929.

Surgeons have observed that patients recently operated on for relief of obstruction of the common bile duct frequently went into severe shock. The syndrome

became known as "liver shock." It nearly always occurs several hours after the surgical procedure and recovery from the anesthetic. It may occur after mere drainage of the gall bladder. The author conducted experiments inquiring into the origin of this condition. He produced experimental obstruction of the common duct in dogs and after certain intervals the liver was removed and extracts made of it. The extracts were sterilized and were injected into other animals, chiefly cats. It was demonstrated that there was an excess of vasodepressor substances in the jaundiced liver, and this excess may be the cause of the clinical shocklike state. The mechanism might be interpreted as being due to the sudden release of pressure on the portal system, so that these substances find their way into the blood stream. Both histamine and choline were found in excess in the jaundiced livers.

N. ENZER.

PERFRINGENS ANTITOXIN AND EXPERIMENTAL INTESTINAL OBSTRUCTION. J. C. OWING and C. A. MCINTOSH, Arch. Surg. **18**:2237, 1929.

The authors conducted several experiments in an effort to determine the inhibitory effect of *Bacillus perfringens* antitoxin on the toxins accumulating in intestinal obstruction, and also experiments to determine the relative toxicity of *B. perfringens* toxin as compared with those occurring in intestinal obstruction. They found that the *B. perfringens* antitoxin had no effect on dogs with obstruction of the upper portion of the small intestines. Also, in those experiments in which they attempted to neutralize the toxins in the isolated intestinal loops with the antitoxin of *B. perfringens,* no success was obtained. In other words, the material in the intestinal loops was just as toxic after the addition of the antitoxin. Dogs immunized against the toxin of *B. perfringens* were just as susceptible to lethal doses of intestinal obstruction toxin. The postmortem observations on dogs dying after the intravenous injection of *B. perfringens* toxin as compared with those dying after the injection of loop toxin showed that there was a greater amount of hemolysis in the former.

N. ENZER.

RELATIVE EFFECTS OF DISTENTION ON DIFFERENT PORTIONS OF THE INTESTINE. C. A. DRAGSTEDT, V. F. LANG and R. F. MILLET, Arch. Surg. **18**:2257, 1929.

This is an experimental study in an effort to determine the effects of distention of the intestine on its own circulation, and also the changes produced by such distention in different portions of the intestinal tract. The experiments were done by injecting air, nitrous oxide gas and mineral oil into the intestinal tract as a whole and into isolated loops. Briefly stated, the effect of this distention on the circulation was more severe in the proximal portion than in the terminal portion; it was greatest in the duodenum and least in the rectum. The effect on the circulation is stasis with resulting pallor and anemia, and finally complete cessation with resulting interference with the nutrition of the wall of the intestine. The duodenum is particularly susceptible to very low pressures. With relatively small increases, varying degrees of damage from cyanosis to infarction may be produced. Anatomically, there would appear to be some explanation for this in that the blood vessels pierce the muscularis in the small intestine at the mesenteric margin, whereas in the large intestine they enter further and further away from the mesenteric border, and come closer to the antimesenteric border. Hence the blood vessels are more superficial in the distal portions of the intestinal tract, and withstand pressure better.

N. ENZER.

A COMPARISON OF THE MANNER OF EXCRETION OF NEUTRAL RED AND PHENOL BY THE FROG'S KIDNEY. JEAN OLIVER and ESHREF SHEVKY, J. Exper. Med. **50**:15, 1929.

Phenol red and neutral red are excreted by the perfused frog's kidney by different routes. Phenol red is excreted chiefly through the glomerulus, neutral

red through the tubules. Some slight excretion of each of these dyes by the converse mechanism is possible, though there is no evidence in our experiments that necessitates such a conclusion. The importance of methods leading to the production of a normal volume of urine by the perfused kidney is emphasized.

AUTHORS' SUMMARY.

STUDIES OF TISSUE MAINTENANCE. PEYTON ROUS and H. P. GILDING, J. Exper. Med. **50**:189, 1929.

The spread of various highly diffusible dyes through the living animal has been utilized as an indicator of the ability of the circulation to serve the tissues under various conditions. The method is direct and searching. Blood service to the viscera, as demonstrated by it, is normally far more profuse than to the skin and muscles, for evident physiologic reasons. After hemorrhages which greatly reduce the blood bulk, service to the viscera is in general still well maintained even though the animal be in extremis. However great the compensatory contraction of the splanchnic vessels may be — and physiologists have long supposed it to be very great — it does not suffice to hinder blood service anywhere in the digestive tract. On the other hand the service to certain unessential abdominal organs (spleen, omentum, urinary bladder) is cut off in large part or wholly; and in comparison with the essential viscera, the skin and most of the skeletal muscles of the bled animal are largely deprived of circulation. This neglect takes a curious form, some regions being still fairly served by the blood while others next them are no longer ministered to. In the skin the areas served, or not served, are highly irregular but are to some extent determined in situation by local pressure factors. Within the muscles the neglect is orderly in arrangement and is largely referable to compensatory vasoconstriction. Certain of the muscles, those used in respiration and in swallowing, furnish significant exceptions to the general rule, being excellently served despite the serious general state. The red bone marrow of the depleted organism continues to be well served by the blood even though situated in limbs that are, for the rest, almost devoid of a circulation. The pregnant uterus also is excellently maintained despite the serious general state. The changes are such as would tend to conserve the forces of the depleted organism and to contribute to its recovery.

AUTHORS' SUMMARY.

STUDIES OF TISSUE MAINTENANCE (THE LIVER AND DIGESTIVE TRACT AFTER HEMORRHAGE). H. P. GILDING, J. Exper. Med. **50**:213, 1929.

The vascular readjustments in compensation for a greatly reduced blood bulk affect the service rendered by the blood to the gastro-intestinal tract and liver far less than they do that to the skin and muscles. Into these latter tissues, india ink is carried almost not at all, whereas it circulates in quantity through the capillaries of the bowel and liver. Evidently vasoconstriction is much less effective in these viscera. Nowhere in them does one find a patchy ischemia like that so widespread in the peripheral tissues. Blood service is maintained to the same extent everywhere throughout the liver even when one of its two sources (hepatic artery or portal vein) is obstructed, and the intrahepatic blood pressure is brought very low. A pronounced patchy ischemia of the stomach and large bowel can be induced by intravenous injection, into normal animals, of sufficient epinephrine to cause the systemic blood pressure to mount to an abnormally high level. Solution of pituitary used in the same way has a greater effect; blood service to the organs mentioned may be completely abolished by means of it. In both instances, though, service to the small intestine and liver is still excellently and evenly maintained.

AUTHOR'S SUMMARY.

HORMONES OF THE FEMALE REPRODUCTIVE CYCLE. E. C. DODDS and F. DICKENS, J. Obst. & Gynaec. Brit. Emp. **36**:92, 1929.

This is a critical review in which the attempt is made to correlate the main facts on which most workers are agreed.

A. J. KOBAK.

BERIBERI AS AN EDEMA DISEASE. J. MEBIUS, Virchows f. path. Anat. **271**:432, 1929.

In four autopsies on patients with beriberi the longitudinal striation of the heart muscle fibers was very distinct while the cross striation was indistinct. There was little intercellular edema, and fatty change was mostly absent. The indistinctness of the transverse striation shows that the normal differences in the water contents of the isotropic and the anisotropic parts of the muscle fiber have disappeared. Since the shifting of fluid from one part into the other is the main factor in muscle contraction (Engelmann), the fatal deficiency of heart muscle function is explained by these observations of indistinct transverse striation. The author explains this and other edematous lesions in beriberi as directly caused by the deficiency in vitamin B. There is no reason to explain the muscle lesions as secondary to nerve lesions. All of the principal symptoms of beriberi can be explained on the basis of muscle lesions.

ALFRED PLAUT.

Pathologic Anatomy

NECROSES OF THE LIVER IN MALARIA. OSCAR KLOTZ, Am. J. Trop. Med. **9**:241, 1929.

Twelve cases of acute malignant malaria were studied in which the parasites (*Paramecium falciparum*) were demonstrated during life. The necroses in the liver at necropsy are described. Similar necroses were found in one case of blackwater fever. The case was one of malarial (*P. falciparum*) blackwater fever. Two other fatal cases failed to show changes although the blood showed large numbers of subtertian parasites.

JOHN PHAIR.

EXPERIMENTAL STUDY OF ACQUIRED RESISTANCE OF THE RABBIT'S RENAL EPITHELIUM TO MERCURIC CHLORIDE. WARREN C. HUNTER, Ann. Int. Med. **2**:796, 1929.

Having previously demonstrated that rabbit's renal epithelium possesses a high degree of resistance to the injurious effects of uranium, Hunter undertook to determine whether or not the renal parenchyma was capable of developing an acquired immunity for mercuric chloride. The minimum lethal dose of sublimate was first determined by subcutaneous and intravenous injections. Immunization experiments were then carried out, starting with small quantities of sublimate and gradually increasing the dosage. Local corrosive action and irregularity of absorption after subcutaneous administration, the danger of thrombosis following intravenous injection, and the excretion in the intestine with the development of a severe enterocolitis, render mercuric chloride an undesirable substance to use for accurate determination of acquired immunity of renal epithelium. Owing to differences in absorption of the sublimate, several injections may be given without producing any demonstrable changes in the renal epithelium, while in other animals the same quantity will produce well marked chronic glomerulotubular nephritis. A slight degree of acquired immunity for sublimate can be demonstrated in regenerated epithelium and glomeruli. A constant observation in the sublimate kidney is the envelopment of necrotic cells by regenerating epithelium.

WALTER M. SIMPSON.

A CASE OF MULTIPLE MYELOMA WITH BENCE-JONES PROTEIN IN THE PLEURAL EFFUSION. E. E. MARCOVICI, Ann. Int. Med. **2**:881, 1929.

Marcovici presents the clinical details of a case of multiple myeloma, presumably involving only the ribs, in which Bence-Jones protein was found in the fluid aspirated from the thoracic cavity before it could be demonstrated in the urine.

WALTER M. SIMPSON.

HEMATOLOGIC STUDY OF THREE GENERATIONS OF A WHITE FAMILY SHOWING ELLIPTICAL ERYTHROCYTES. W. C. HUNTER and R. B. ADAMS, Ann. Int. Med. **2**:1162, 1929.

The erythrocytes of one male parent, all of his eight children, and three of his grandchildren showed elliptical morphology. After studying sealed fresh preparations of blood over long intervals and exposing the cells to carbon dioxide, the authors conclude that this morphologic abnormality is not of the type seen in sickle cell anemia. Several of the subjects showed some degree of anemia.

WALTER M. SIMPSON.

BRONCHOGENIC SQUAMOUS CELL CARCINOMA. RALPH G. MILLS and NOLIE MUMEY, Arch. Int. Med. **43**:516, 1929.

A detailed report is given of a case in which there was reason to suspect infection with *Endameba histolytica,* but which proved to be a bronchogenic carcinoma associated with hydrothorax, mucoid infiltration of the lung and disease of the gallbladder and kidney.

Certain cells, when observed on the warm stage, manifested activity and assumed morpholoic forms that might readily lead to confusion with amebas.

Cells of the human body, especially histiocytes, under pathologic conditions simulated amebas when viewed in sections stained either with hematoxylin and eosin or with iron hematoxylin.

One case does not justify sweeping conclusions, but the intensive study of this case involved extensive search of the literature and was made against a background of many years of work in parasitology. Therefore, it is safe to conclude that if there is doubt as to a given cell in the body being an ameba, it probably is not. Disregard of this criterion may lead to further erroneous conclusions.

AUTHORS' SUMMARY.

ENCEPHALITIS PERIAXIALIS DIFFUSA. WALTER D. SCHELDEN, JOHN B. DOYLE and JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **21**:1270, 1929.

A clinical and pathologic report of two cases of so-called Schilder's disease is made by Schelden and his co-workers.

In both cases the macroscopic changes were characteristic of Schilder's disease: large areas of degeneration of the subcortex, absence of involvement of the gray matter of the cortex or only of its deeper layers. The degeneration in this disease usually starts in the occipital, but may also start in the frontal lobe.

Microscopic changes were: early breaking up of the myelin, followed by that of the axons which generally suffer less severely; both the myelin and axons break up into smaller fragments and become finally transformed into lipoids which are taken up by scavenger cells (gitter cells). The glia shows marked progressive changes, especially in the form of proliferation of astrocytes and the appearance of large numbers of giant cytoplasmic cells ("gemästete") glia cells. It is remarkable that the type of glia cells known as oligodendroglia showed in these cases regressive changes in the form of so-called swollen oligodendroglia. A wall of hyperplastic astrocytes was seen between the degenerated and the normal tissues. Microglia was abundant and satellitosis was present in the advanced stages. So-called mucocites, that is, cells containing mucus, were absent but were present within the perivascular spaces. These contained masses of scavenger cells mixed with lymphocytes, few polymorphonuclear cells but no plasma cells. It is evident that in contrast to the gross pathologic changes, the microscopic picture of Schilder's disease shows nothing specific, nor is the clinical picture characteristic. However, in the first patient, a boy aged 7 years, the diagnosis has been made before the patient's death, from the following symptoms: apathy, change of personality, rapid onset of blindness and deafness, bulbar symptoms with signs of involvement of the motor and sensory neurons and frequent convulsions. The course was rapid. The patient died four months after the onset. Previous diseases were various

infectious diseases of childhood and preceding the onset there was a bilateral otitis media.

In the second case, the patient was a woman, aged 27. Six and one-half weeks prior to admission to the hospital she had been delivered of her first child by forceps; two and a half weeks later visual disturbances set in — blurring of vision followed by complete blindness within one week; later, facial weakness developed with weakness and partial paralysis of the left side of the body; generalized tremor, involuntary evacuations and coma. Death followed two months after onset. Here the actual condition was not recognized and an abscess of the brain was considered probable. A craniotomy was done but no abscess was found.

G. B. HASSIN.

EPENDYMOMAS. EDGAR F. FINCHER, JR., and GAYLORD P. COON, Arch. Neurol. & Psychiat. **22**:19, 1929.

Fincher and Coon state that tumors of ependymal origin are rare. In an analytic study of 140 gliomas eight were found to be tumors of cells of ependymal derivation. The largest number have been located in the posterior fossa in close proximity to the fourth ventricle. Ependymomas are slowly growing tumors. They tend, according to Bailey and Cushing, to extend down the spinal cord. In this they differ from medulloblastomas, which seldom do so. They are very cellular, the nuclei being spherical or oval; the cell body is coarsely granular and polygonal. Some cells are ependymal spongioblasts. When these predominate they encircle the blood vessels from which they are separated by a clear zone. In suitably stained specimens this is filled with the processes of the embryonic cells. They contain so-called blepharoplasts — minute, deeply staining granules surrounded by clear halos within their cytoplasm.

In the eight cases studied, the majority of the ependymomas were situated in the cerebrum close to the lateral ventricles, whereas this type of glioma is most commonly found in the posterior fossa.

Grossly the tumors were reddish gray, encapsulated, lobulated and moderately firm. On the surface of the majority of these tumors were cysts varying in size from 1 to 4 cm., containing thin yellow fluid which did not coagulate (in two cases it was removed on exposure to the air). In this respect the fluid strikingly differed from that found in other gliomatous cysts. The presence of ependymal spongioblasts, when stained with Hortega's silver carbonate methods, is of great diagnostic value. Some tumors had centers of calcareous deposits which were distinct enough to show in x-ray pictures.

In two cases (6 and 7) incomplete removal of the tumor was accomplished. No return of the symptoms was noted after a lapse of fourteen and thirteen months, respectively. The ependymomas of the cerebrum generally offer a favorable prognosis.

G. B. HASSIN.

PYRAMIDOPALLIDAL DEGENERATION SYNDROME DUE TO MULTIPLE SCLEROSIS. J. M. NIELSEN, D. C. WILSON and R. R. DIETERLE, Arch. Neurol. & Psychiat. **22**:45, 1929.

In a man, aged 50, symptoms indicative of a typical pyramidal lesion of the lower extremities (weakness, spasticity, exaggerated tendon reflexes, absent abdominal reflex, Babinski and similar signs) were associated with signs and symptoms (tremor, parkinsonian attitude) of an extrapyramidal lesion of the upper extremities, chin and head. Many other symptoms were present, such as parosmia, scotomas, mild sensory and bladder disturbances. There was a remission of one or two years' duration. The course was atypical; the majority of symptoms began first on one side, and then affected the other, while the ordinary classic signs of multiple sclerosis (ocular symptoms, speech, intention tremor) were absent. A diagnosis of multiple sclerosis was considered, but was rejected. Necropsy, however, revealed this condition. The authors conclude that a combined pyramidal and

extrapyramidal lesion may be produced not only by arteriosclerosis, lesion of the basal ganglia and epidemic encephalitis but also by multiple sclerosis.

G. B. HASSIN.

THE HISTOGENESIS OF VON RECKLINGHAUSEN'S DISEASE. S. H. GRAY, Arch. Neurol. & Psychiat. **22**:91, 1929.

In two typical cases of von Recklinghausen's disease, sarcomatous changes took place. In one of these cases Gray studied serially several small tumors which were attached to the phrenic and intercostal nerves. The sections included some parts of the uninvolved nerve contiguous to the small tumors. He illustrates his views and conclusions with ten photographs and photomicrographs. His conclusions are that "there can be no question" that in his two cases of von Recklinghausen's disease, a relationship between the cells of the sheath of Schwann and those comprising the tumors does not exist; that the tumor arose not from the embryonic cells of Schwann, as advocated by Verocay, but from the perineural connective tissue. Such a view, he maintains, is supported by the character of the tumor cells themselves and especially by the character and metastatic formation of the sarcomatous nodules.

G. B. HASSIN.

STUDIES ON INFLAMMATION. VALY MENKIN, J. Exper. Med. **50**:171, 1929.

Trypan blue injected into normal subcutaneous tissue passes rapidly to the regional lymphatic node and is found in lymph drawn from its efferent lymphatic. When the dye is injected into the normal peritoneal cavity it rapidly appears in the lymph of the retrosternal lymphatics and stains deeply the retrosternal lymphatic nodes. Trypan blue injected into the site of inflammation in the subcutaneous tissue or in the peritoneal cavity is fixed in the inflamed area and fails to reach the regional lymphatic nodes. If an inflammatory reaction has been produced in the dermis or in the subcutaneous tissue, trypan blue injected into the circulating blood enters the site of inflammation and is fixed so that the tissues are deeply stained.

AUTHOR'S SUMMARY.

THE EFFECT OF UNILATERAL NEPHRECTOMY ON THE TOTAL NUMBER OF OPEN GLOMERULI IN THE RABBIT. ROBERT A. MOORE and GREGORY F. LUKIANOFF, J. Exper. Med. **50**:227, 1929.

Under the experimental conditions employed, from 44 to 78 per cent of the glomeruli of the normal rabbit kidney contain circulating blood at any one moment. After unilateral nephrectomy, the number of glomeruli in the remaining kidney which contain circulating blood is increased to 91 to 99 per cent. Compensation for the removal of one kidney is accomplished during the first ten days at least, by an increase of the number of open glomeruli in the opposite kidney.

AUTHORS' SUMMARY.

THE LESIONS IN THE SKELETAL MUSCLES IN EXPERIMENTAL SCORBUTUS. GILBERT DALLDORF, J. Exper. Med. **50**:293, 1929.

Muscle degeneration was constantly found in the intercostal muscles of scorbutic guinea-pigs. It has likewise been found in the masseter and diaphragmatic muscles. Exercise will produce an identical lesion in other skeletal muscles in scorbutic animals. The lesions appear to be an intrinsic part of the scorbutic process. It is suggested that the tenderness over muscles in scorbutic animals and in man may be due to this myopathy.

AUTHOR'S SUMMARY.

IRREGULAR UTERINE HEMORRHAGE. WILFRED SHAW, J. Obst. & Gynae. Brit. Emp. **36**:1, 1929.

Shaw's paper is based on a thorough study of 200 consecutive cases of irregular uterine hemorrhage (exclusive of obvious causes such as tumors and diseases of

adjacent organs), in which the endometrium, and in many of the cases the uterus and ovaries likewise were available for study. It is shown that the terms "endometritis" and "metritis" are too loosely used and that the inflammatory processes are only assumptions. Shaw finds these conditions rather rare, and when present, resemble the inflammatory processes found in other organs. Involution of the puerperal uterus was studied by means of Weigert van Gieson stain. Shaw disagrees with Goodall's original conception that the involuting vessel is replaced by a newer vessel growing into the lumen of the old one. During puerperium a subendothelial proliferation, or swelling, and a granular atrophy of the muscle fibers take place in the arteries. The veins and placental sinuses undergo similar processes in involution. Hyaline degeneration of the media takes place which, through swelling and distortion, reduces the caliber of the vessel. The subendothelium also swells. Elastic tissue is deposited around the blood vessels and between the muscle bundles. This tissue increases with each pregnancy. The deposit of elastic tissue around the veins, and in the media and external elastic lamina of the arteries may give the impression of a new vessel forming within the older one. During subinvolution the formation of elastic tissue appears to be retarded. Some connective tissue is also laid down around the vessels and between the muscle bundles. No cases were noted in which a large amount of elastic tissue was associated with irregular uterine hemorrhage; and no condition was found in the menstruating women in which the muscle cells are replaced by fibrous tissue. Shaw concludes, therefore, that neither subinvolution nor a fibrotic state of the uterus are underlying factors in causing irregular uterine hemorrhage. A large group of cases having irregular uterine hemorrhage are associated with ovarian dysfunctions in which the full development of the corpus luteum is inhibited and the follicle becomes cystic. In these cases the endometrium is hyperplastic, the glands cystically dilated and the superficial surface necrotic. Another group of menstrual disorders occur when the ovaries are shrunken and have hemorrhagic follicles projecting over their surfaces. The endometrium in these cases is hyperemic and edematous. Other cases of menstrual disturbances not as definite in character nor as numerous as those in the aforementioned two groups are also found to be associated with disease of the ovaries. Shaw prefers to consider all cases of irregular uterine hemorrhage that are not secondary to obvious disease of the endometrium under the heading of metropathia.

A. J. KOBAK.

A LARGE FATTY TUMOR OF THE UTERUS. JOHN WEBSTER BRIDE, J. Obst. & Gynaec. Brit. Emp. **36**:83, 1929.

A 9 pound (4 Kg.) oval tumor of the uterus, which was removed under the impression that it was a fibromyoma, is reported because of its rarity. The patient was a multipara, aged 63, whose chief complaint was severe vaginal bleeding occurring after the menopause. The author conceives this tumor to have originated from a large fibroid.

A. J. KOBAK.

LIPOMA OF FALLOPIAN TUBE. SAMPOERNO, Ztschr. f. Gynäk. **53**:1123, 1929.

Benign nonepithelial tumors of the fallopian tube are rare. The first lipoma was apparently reported in 1921; since that time two others have been recorded. The one reported by the author occurred in a woman, aged 52, and was a chance finding in the adnexa of a uterus removed for carcinoma. The tumor was situated near the fimbriated end. The fimbriae and ostium were normal. The nodule was about the size of a cherry, sharply delimited and encapsulated. Its lipomatous character was evident in the gross. Microscopically it was composed of adipose tissue, which was subdivided by strands of fibrous tissue. The tumor was subserous, as was the case in the first lipoma to be recorded, whereas the remaining two were submucous and polypoid.

O. T. SCHULTZ.

FIBROMYOMA OF FALLOPIAN TUBE. A. W. HOCHLOFF, Ztschr. f. Gynäk. **53**: 1125, 1929.

Dietrich, in 1926, was able to collect thirty-eight cases of fibromyoma of the fallopian tube. The example recorded by Hochloff occurred in a woman, aged 35, who had complained of periodic attacks of pain in the right inguinal region for ten years. The pain bore no relation to menstruation. The last previous attack of pain before admission had lasted three days. A mass the size of an apple could be palpated to the right of the uterus. The preoperative diagnosis was cyst of the ovary. At operation the proximal portion of the right tube, which formed the pedicle of the tumor mass, was found twisted on itself. The tumor, which was attached to the ampullary portion of the tube, measured 7 by 5 by 6 cm. and weighed 285 Gm. It was composed of smooth muscle and fibrous tissue and was somewhat edematous from partial strangulation. There was no sharp delimitation between the muscle of the tube wall and that of the tumor. Most of the previously recorded fibromyomas have arisen from the interstitial portion of the tube, only one other case of ampullary tumor being noted by Dietrich. The largest previously reported fibromyoma of the tube weighed 3,000 Gm.

O. T. SCHULTZ.

HEMORRHAGES OF THE LARGE ARTERIES IN CARCINOMA OF THE ESOPHAGUS AND STOMACH AND FUSOSPIROCHAETAL INFECTION. K. WOLKOFF and W. D. ZINSERLING, Ztschr. f. Krebsforsch. **28**:449, 1929.

In six cases of hemorrhage of the large arteries occurring in association with carcinoma of the esophagus or stomach, the vascular rupture was found to be caused not by tumor infiltration, but by gangrene caused by infection with associated fusiform bacilli and spirochetes.

H. E. EGGERS.

Pathologic Chemistry and Physics

ENDOGENOUS URIC ACID AND HEMATOPOIESIS. J. KRAFKA, JR., J. Biol. Chem. **83**:409, 1929.

The endogenous uric acid may arise from the extruded nuclei of the normoblasts on the maturation of the erythrocytes. More than 29 cc. of red corpuscles are produced daily, in the normal man, together with about 29 Gm. of extruded nuclear material. The uric acid equivalent of the latter is 4.23 Gm., a quantity many times larger than that excreted during maintenance on a purine-free diet. The output of endogenous uric acid is greatly increased following severe hemorrhage, reaching a maximum on the second day, just preceding the period of marked reticulocyte increase.

ARTHUR LOCKE.

THE STORAGE OF MANGANESE AND COPPER IN THE ANIMAL BODY AND ITS INFLUENCE ON HEMOGLOBIN BUILDING. R. W. TITUS and J. S. HUGHES, J. Biol. Chem. **83**:463, 1929.

Both manganese and copper may be essential supplements to iron in the vital synthesis of hemoglobin.

ARTHUR LOCKE.

BIOMETRY OF CALCIUM, INORAGNIC PHOSPHORUS, CHOLESTEROL, AND LECITHIN IN THE BLOOD OF RABBITS. EFFECTS OF A MALIGNANT TUMOR. ALVIN R. HARNES, J. Exper. Med. **50**:109, 1929.

Experiments are reported in which it was shown that the calcium, inorganic phosphorus, cholesterol and lecithin in the blood of normal rabbits were influenced by inoculation with a malignant tumor. Animals in which death was due to tumor gave results on which the following conclusions are based: A marked increase in inorganic phosphorus of blood serum and cholesterol of whole blood followed inoculation. The ratios of cholesterol to calcium and lecithin to calcium increased

in trend, while the calcium to inorganic phosphorus, lecithin to cholesterol, and lecithin to inorganic phosphorus ratios showed a marked decrease in trend. The cholesterol-lecithin were all negative.

AUTHOR'S SUMMARY.

THE ION CONTENT OF GASTRIC FLUID. E. SCHAIRER, Klin. Wchnschr. **8**:1113, 1929.

The human gastric fluids contain appreciable amounts of K which calculated as Cl is approximately 11.4 per cent of the total chloride, and is not changed much during secretion in the same person. With increasing acid secretion the Na content of the gastric fluids diminishes, and in hypo-acidity or anacidity it is proportionately markedly increased, the K content unchanged, and consequently the ratio Na to K is altered in favor of the Na. In hypo-acidity and normal acidity the neutral salt content in contrast to the MCl content is not appreciably diminished.

AUTHOR'S SUMMARY.

THE FERMENT ACTIVITY OF MUSCLE TISSUE FROM A MUMMY OF 3,000 YEARS AGE. E. SEHRT, Klin. Wchnschr. **8**:1177, 1929.

The macroscopic oxidase reaction with muscle tissue from a mummy of 3,000 years age was strongly positive.

AUTHOR'S SUMMARY.

THE ELECTROLYTE CONTENT OF SERUM IN HEART AND VASCULAR DISEASES. J. TEPLOFF and A. KOSCHEWNIKOWA, Klin. Wchnschr. **8**:1222, 1929.

In heart and vascular diseases without insufficiency of circulation there is no variation in the Ca content. The K content usually is normal, sometimes it is increased, but the ratio K/Ca remains constant. During cardiac decompensation in most patients there is a diminution of the Ca content as well as the Cl and the inorganic P. The K content remains within the limits of normal. On the appearance of cardiac insufficiency especially with cardiosclerosis the relation between K and Ca in the serum varies from the normal and usually in an increase.

AUTHORS' SUMMARY.

THE RESERVE ALBUMIN OF THE LIVER. K. PASCHKIS, Klin. Wchnschr. **8**:1293, 1929.

Rats on a high albumin diet are particularly resistant to insulin. The albumin granules of the liver disappear with large doses of insulin. Epinephrine also decreases the reserve albumin. Epinephrine and insulin combined have no effect on the reserve albumin. Possibly these substances affect metabolism differently. The reserve albumin is not influenced by thyroidin. Thymic preparations seem to favor storage of albumin.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

MENINGOCOCCUS ENDOCARDITIS. H. E. MACMAHON and E. A. BURKHARDT, JR., Am. J. Path. **5**:197, 1929.

A case of meningococcus endocarditis is reported with the autopsy and bacteriologic observations. A brief discussion deals with the clinical, pathologic and bacteriologic considerations of meningococcus endocarditis. The literature is reviewed.

AUTHORS' SUMMARY.

A CASE OF MENINGITIS DUE TO ENDOMYCES CAPSULATUS (NEW SPECIES). ALLAN G. REWBRIDGE, CARROLL W. DODGE and THEODORE T. AYERS, Am. J. Path. **5**:349, 1929.

The clinical record and autopsy observations in a case of meningitis due to *Endomyces capsulatus* are reported. The organism was not found in the spinal

fluid. The morphologic and cultural characteristics of *Endomyces capsulatus* are described. The organism is pathogenic for mice but not for rabbits or guinea-pigs.

AUTHORS' SUMMARY.

THE PRESERVATION OF YELLOW FEVER VIRUS. W. A. SAWYER, W. D. M. LLOYD and S. F. KITCHEN, J. Exper. Med. **50**:1, 1929.

The virus of yellow fever may be preserved for at least 154 days in the blood or liver tissue of infected monkeys if the material is dried in a vacuum while in the frozen state and kept in the refrigerator in sealed glass containers. A gradual diminution of virulence is noticeable in the older specimens. If infectious blood is dried in a vacuum at room temperature, instead of in the frozen state, and is stored in sealed containers in the refrigerator, the virus may survive as long as 155 days. The virus may be preserved for at least thirty days in liver kept continuously frozen. Storage of blood or liver in 50 per cent glycerin in the refrigerator will usually keep the virus alive for sixty days and may do so for 100 days, but with the injection of the older material there is a marked tendency toward lengthening of the incubation period and increase in the number of recoveries. Yellow fever virus in citrated or clotted blood, when kept in the refrigerator, dies out rapidly. In our experience the most satisfactory method of preserving strains of yellow fever virus in the laboratory, consists of freezing and drying blood taken from a monkey on the first day of an attack of experimental yellow fever and storing the dry material in sealed glass tubes in a cold place.

AUTHORS' SUMMARY.

FURTHER NOTES ON THE FILTRATION OF THE VIRUS OF VACCINIA. HUGH K. WARD, J. Exper. Med. **50**:31, 1929.

An active filtrate can be obtained from vaccinia lesions by grinding up the fresh tissue with glass fragments, emulsifying in hormone broth, centrifuging the emulsion and filtering the supernatant fluid through a Berkefeld V filter. The sterile filtrate so obtained has been shown by comparative titration on rabbits to have about one sixteenth of the activity of the nonsterile emulsion used in vaccination of human beings. Centrifugation of such a filtrate shows a partial concentration of the virus in the lowermost layer. The virus survives for a long time, if the filtrate is kept near the freezing point, and probably will survive indefinitely if kept frozen. The addition of glycerin is not necessary.

AUTHOR'S SUMMARY.

ATTEMPTS TO REPRODUCE RHEUMATIC FEVER IN ANIMALS. LOUIS GROSS, LEO LOEWE and BENJAMIN ELIASOPH, J. Exper. Med. **50**:41, 1929.

Experiments have been described in which we attempted to reproduce in animals the lesions characteristic of rheumatic fever in man. A large number of animals representing seven species was employed. Among other materials streptococci isolated in pure culture from the blood of rheumatic patients (proved to be so by biopsy or by autopsy) as well as whole blood, plasma, serum, pericardial, pleural and hydrocele fluid, filtrates from tonsils, subcutaneous nodules, lymph nodes and nasopharyngeal washings obtained from such patients were used in a variety of combinations and with a number of procedures calculated to predispose the animal to the disease. A discussion is given of the criteria the fulfilment of which is essential for the establishment of the experimental production of rheumatic disease in animals. Judged by these criteria, we have failed to reproduce the disease. This conclusion, we believe, holds true for all the work thus far reported in the literature.

AUTHORS' SUMMARY.

ON THE RELATION OF BACTERIA TO SO-CALLED "CHEMICAL PNEUMONIA." A. R. KOONTZ and M. S. ALLEN, J. Exper. Med. **50**:67, 1929.

The question of a causal relation of the bacteria in gassed lungs to the pneumonia present cannot be regarded as decided. It may be said that the appearance

of gassed lungs in patients with pneumonia is similar to that in pneumonia of known bacterial origin. In a few cases the type of pneumonia found coincides with the reported cases of so-called "chemical pneumonia," which is characterized by a preponderance of epithelial cells in the exudate. Gassed lungs are not sterile but show highly varying numbers of bacteria. The bacteria are not intracellular and are not present in large numbers in the majority of cases. The arguments for and against a causal relationship between the bacteria and the pneumonia may be summarized. Against a causal relationship are: (1) the early appearance of pneumonia after gassing; (2) the occurrence of pneumonia with small numbers of bacteria present, and (3) the fact that few bacteria are engulfed by leukocytes in gassed lungs, whereas large numbers are present in the pneumonias in nongassed subjects and are conspicuously intracellular. In favor of a causal relationship are: (1) the presence of bacteria in any numbers; (2) the picture of bronchopneumonia presented is similar to bronchopneumonia of known bacterial origin, and (3) pneumonias characterized by large numbers of epithelial cells in the exudate (so-called "chemical pneumonia") occur in animals that were never gassed or subjected to other irritating substances in any way.

AUTHORS' SUMMARY.

STUDIES ON SOUTH AMERICAN YELLOW FEVER. NELSON C. DAVIS and RAYMOND C. SHANNON, J. Exper. Med. **50**:81, 1929.

Yellow fever virus from *M. rhesus* has been inoculated into a South American monkey (*Cebus macrocephalus*) by injection of blood and by bites of infected mosquitoes. The *Cebus* does not develop the clinical or pathologic signs of yellow fever. Nevertheless, the virus persists in the *Cebus* for a time as shown by the typical symptoms and lesions which develop when the susceptible *M. rhesus* is inoculated from a *Cebus* by direct transfer of blood or by mosquito (*A. aegypti*) transmission.

AUTHORS' SUMMARY.

THE RÔLE OF CARBOHYDRATES IN BIOLOGICAL OXIDATIONS AND REDUCTIONS. EXPERIMENTS WITH PNEUMOCOCCUS. RENÉ DUBOS, J. Exper. Med. **50**:143, 1929.

The reducing power of plain broth cultures of pneumococcus is largely dependent on the presence in the medium at the time when the reduction test is performed of certain metabolities. The washed cells of pneumococcus are able to reduce the various indicators of oxidation-reduction potentials in the presence of dextrose. The relative velocity of reduction of these indicators is determined by the number of cells used in the test, the concentration of the dyes and their position in the oxidation reduction scale. Oxidized thiol compounds (glutathione, cystine, oxidized thioglycollic acid) are likewise rapidly reduced by dextrose in the presence of washed cells of pneumococcus. This pneumococcus-dextrose system is able to form peroxide under aerobic conditions. These substances which form peroxide in the presence of pneumococcus cells are also the ones which Cole found to be active in changing hemoglobin into methemoglobin under the same conditions. The power of washed cells of pneumococcus to reduce methylene blue in the presence of dextrose is dependent on at least two constituents: one which can be readily removed from the cell by washing. Sugar-free meat infusion will function instead of it. The other is inactivated more slowly by the process of washing and is destroyed by heating for ten minutes at 55 C. The interreaction between the dextrose and the cell seems to result in a fundamental reaction in which one molecule of dextrose becomes able to reduce rapidly one molecule of methylene blue. The existence of side-reactions often obscures this ratio. The significance of these observations is considered in relation to the nature and mechanism of the "activation" of metabolites, the preparation of synthetic mediums, the phenomena of growth and the meaning of the expression "reducing power of a bacterial culture."

AUTHOR'S SUMMARY.

PERSISTENCE OF LIVING CELLS IN MAITLAND'S MEDIUM FOR THE CULTIVATION OF VACCINE VIRUS. T. M. RIVERS, E. HAAGEN and R. S. MUCKENFUSS, J. Exper. Med. **50**:181, 1929.

Cells survive for at least five days and at times are capable of multiplying in a mixture of serum and Tyrode's solution used by Maitland for the cultivation in vitro of vaccine virus.

AUTHORS' SUMMARY.

A STUDY OF PNEUMONIA IN A RURAL AREA IN SOUTHERN ALABAMA. W. G. SMILLIE and E. L. CALDWELL, J. Exper. Med. **50**:233, 1929.

Pneumococcus type IV of low virulence was the prevailing organism in fifty-eight cases of pneumonia studied in southern Alabama. Fixed types of pneumococci were not common. Pneumonia was more prevalent in children from 5 to 15 years of age than in adults. As a rule, the disease ran a mild course. In most of the cases of pneumonia the patients gave a definite history of an acute cold antedating the attack of pneumonia by a period of from five to eight days. Exposure alone did not seem to predispose to pneumonia, but those with an acute cold who were exposed to chilling of the body surface frequently developed pneumonia. There were seven "family epidemics" of pneumonia. In each instance there was a family epidemic of colds antedating the pneumonia. The pneumococcus was found in large numbers in the nasopharynx of those suffering from colds as well as in the pneumonia patients. The epidemiology of pneumonia in the pioneer days of American history has many points in common with the epidemiology of pneumonia in a rural isolated area in southern Alabama today. This suggests that the crowded conditions and frequent contracts of modern city life have built up a community resistance to avirulent strains of pneumococci.

AUTHORS' SUMMARY.

DISSOCIATION OF HOG BACILLUS. C. P. LI, Exper. Med. **50**:245 and 255, 1929.

Four forms of the hog cholera bacillus are described, namely the "normal" type strain, and three variants.

THE EFFECT OF CATAPHORESIS ON POLIOMYELITIS VIRUS. P. K. OLITSKY, C. P. RHOADS and P. H. LONG, J. Exper. Med. **50**:273, 1929.

Under ordinary conditions of hydrogen ion concentration the virus of poliomyelitis, as such, or associated with particles in fine suspensions, migrates in an electrical field to the anode. It follows that the virus bears an electronegative charge. By means of cataphoresis, the virus can be recovered from a noninfective mixture of virus and specific immune serum. By the same means it is possible to reveal the presence of virus in the central nervous system of a monkey which has recovered from the active stage of experimental poliomyelitis.

AUTHORS' SUMMARY.

ADAPTATION OF MASTITIS STREPTOCOCCI TO MILK. F. S. JONES and H. S. SIMMS, J. Exper. Med. **50**:279, 1929.

The data here presented indicate that the inhibitory principle affecting the growth of stroptococci in milk is not greatly utilized during the lag phase, and that the abrupt termination of lag is not due to the utilization of the principle. They further indicate that the sudden beginning of growth cannot be ascribed to a resistant type of streptococcus present in the culture from the first, but to an adaptation occurring during the leg phase. The addition of large numbers of dead or living streptococci to milk, for limited periods, fails to diminish appreciably the inhibitory principle.

AUTHORS' SUMMARY.

THE EFFECT OF EXTRACTS OF ORGANS ON THE INFECTING POWER OF VACCINE VIRUS. F. DURAN-REYNALS, J. Exper. Med. **50**:327, 1929.

Brain and testicle tissue from immune rabbits brought in contact with the Levaditi or Noguchi strains of vaccine virus will fix or inactivate the virus. Extracts of normal testicles from susceptible animals enhance to an extraordinary degree the infectivity of both the neuro and the dermal strains of vaccine virus. The Noguchi virus is not affected by testicle extracts when injected into the skin, but kidney extract has a definite enhancing power on the strain when injected into either skin or testicle. The effect of tissue extracts seems to be on the cells of the host rather than on the virus. This is indicated by the fact that virus injected intravenously localizes most readily in an area of skin previously injected with testicle extract. Furthermore an enhanced lesion results if the virus is injected into an area as long as three days after the area has been injected with testicle extract. The augmenting substance of the tissue extracts is little affected by high dilutions, passes through a Berkefeld V candle and is carried down with the proteins precipitated by weak acids. Rabbits with enhanced lesions show general symptoms and about 25 per cent die with generalized vaccinia. Kidney, and probably skin, brain and liver extracts possess enhancing properties, but to a much less degree than the testicle. On the other hand, spleen, blood and probably lymph nodes and bone marrow not only fail to produce enhancement, but actually restrain or even suppress entirely the vaccinal skin infection.

AUTHOR'S SUMMARY.

A STUDY OF THE GENERALIZATION OF VACCINE VIRUS FROM ENHANCED SKIN LESIONS. FRED W. STEWART and F. DURAN-REYNALS, J. Exper. Med. **50**:341, 1929.

Rabbits bearing intensive skin lesions resulting from the intracutaneous injection of neurovirus plus testicular extract show typical histologic alterations in the gonads, suprarenal glands, liver, spleen, lung, lymph nodes and bone marrow. Similar but less widespread alterations are found after intravenous injection of neurovirus. Although testicle extract injected intracutaneously with neurovirus has a marked enhancing action on the activity of the latter, the same mixture injected intravenously yields no sign of any such enhancement. The significance of these observations as regards the question of the ectodermotropism of vaccine virus is discussed, and the doctrine of specific organ affinites is considered.

AUTHORS' SUMMARY.

PARALYSIS IN GUINEA-PIGS BY THE TUBERCLE BACILLUS. PAUL A. LEWIS and RICHARD E. SHOPE, J. Exper. Med. **50**:365, 1929.

When a strain of human tuberculosis was carried from guinea-pig to guinea-pig by intracerebral inoculation, the bacillus of tuberculosis could be readily recovered in the semisolid *Leptospira* medium of Noguchi simply modified by the substitution of guinea-pig for rabbit serum. Whether even this modification is required remains to be determined. The tubercle bacillus in these cultures and possibly in the nerve tissue as well differed from the classic type in that it was less acid-fast and lacking in alcohol fastness. However, it retained the Gram stain as modified by Much. Staining reactions, as this culture of the tubercle bacillus shows, are not absolute qualities but are variable with conditions, a consideration which it may be important to recognize. Efforts to define these conditions more precisely are likely to be productive.

AUTHORS' SUMMARY.

LECITHIN AND STREPTOCOCCAL HEMOLYSIN. J. GORDON and F. R. STANSFIELD. Brit. J. Exper. Path. **10**:191, 1929.

Lecithin added to cultures of hemolytic streptococci neutralizes the hemolytic activity. Treatment with ligroine does not remove or destroy hemolysin. The hemolytic activity of streptococcal cultures cannot be restored by treatment with a lecithin solvent (ligroine) after it has once been destroyed by addition of lecithin.

AUTHORS' SUMMARY.

NOTES ON INFECTIOUS MYXOMATOSIS OF RABBITS. G. M. FINDLAY, Brit. J. Exper. Path. **10**:214, 1929.

The symptoms and pathologic changes in infectious myxomatosis of rabbits are described. In the connective tissue cells of the lesions certain minute granules are present which may possibly represent the actual virus.

AUTHOR'S SUMMARY.

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF B. INFLUENZAE. ALEXANDER FLEMING, Brit. J. Exper. Path. **10**:226, 1929.

A certain type of *Penicillium* produces in culture a powerful antibacterial substance. The antibacterial power of the culture reaches its maximum in about seven days at 20 C. and after ten days diminishes until it has almost disappeared in four weeks. The best medium found for the production of the antibacterial substance has been ordinary nutrient broth. The active agent is readily filtrable and the name "penicillin" has been given to filtrates of broth cultures of the mold. Penicillin loses most of its power after from ten to fourteen days at room temperature but can be preserved longer by neutralization. The active agent is not destroyed by boiling for a few minutes, but in alkaline solution boiling for one hour markedly reduces the power. Autoclaving for twenty minutes at 115 C. practically destroys it. It is soluble in alcohol but not in ether or chloroform.

The action is marked on the pyogenic cocci and the diphtheria group of bacilli. Many bacteria are insensitive, e.g. the coli-typhoid group, the influenza-bacillus group and the enterococcus. Penicillin is nontoxic to animals in enormous doses and is nonirritant. It does not interfere with leukocytic function to a greater degree than does ordinary broth. It is suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with microbes sensitive to penicillin. The use of penicillin on culture plates renders obvious many bacterial inhibitions which are not evident in ordinary cultures. Its value as an aid to the isolation of *B. influenzae* has been demonstrated.

AUTHOR'S SUMMARY

CRITICISM OF RANKE'S TEACHING OF THE STAGES IN TUBERCULOSIS, PARTICULARLY OF RANKE'S SECONDARY STAGE. W. BLUMENBERG, Beitr. z. klin. d. tuberk. **71**:385, 1929.

This paper is primarily a rather violently polemic criticism of Ranke's concepts. The refutation of Ranke's work is, in part, of a highly theoretical nature and unsuitable for reproduction in a short abstract. The author's points of view are supported by observations at autopsy in a rather large number of cases, some of which are reported in detail. The conclusions are that Ranke's teachings are wrong in toto, and that it is impossible to differentiate various stages in the development of tuberculosis.

MAX PINNER.

PHTHISIS OF THE SUBPLEURAL LYMPH NODES. F. SCHMÖE, Beitr. z. klin. d. Tuberk. **71**:449, 1929.

Subpleural lymph nodes constitute, normally, an important connecting link between the superficial and the deep lymphatic system of the lung. On account of their location, they play an important rôle, both in aërogenous and hematogenous propagation of tubercle bacilli. Subpleural lymph nodes, in the vicinity of primary foci, may become infected and present, then, the picture which is known in the primary complex of lymph glands. These glands, however, become much more frequently involved if a hematogenous spread occurs subsequent to the primary infection, that is in endogenous reinfection. In such cases, these lymph glands present the histologic picture which is characteristic for reinfection foci. The subpleural lymph glands protect the greater circulation from hematogenous infection. It is pointed out that tuberculous scars in these lymph nodes are sometimes the only demonstrable reinfection foci.

MAX PINNER.

PERIFOCAL HEMORRHAGES IN TUBERCULOSIS. L. SIMONSON, Beitr. z. klin. d. Tuberk. **71**:467, 1929.

In four cases of tuberculosis, in different organs, hemorrhages in the immediate vicinity of tuberculous foci are reported. They are probably the result of several factors, such as stasis, specific toxins and allergy.

MAX PINNER.

A CASE OF SEPSIS TUBERCULOSA GRAVISSIMA (AVIAN TUBERCULOSIS?). M. DUGGE, Beitr. z. klin. d. Tuberk. **71**:538, 1929.

A woman, aged 65, died three days after admission and eleven days after the onset of clinical symptoms. The symptomatology was of such a nature that typhoid fever was diagnosed, although serologic and bacteriologic tests were negative. At autopsy, many tumor-like nodules were found scattered throughout the spleen and liver. The mesenteric and bronchial lymph nodes were much enlarged. There were many emboli in the smaller branches of the pulmonary artery. Histologically, it was found that all the nodules consisted of focal necroses which contained large numbers of acid-fast rods. Microscopic foci of similar nature were found in the stomach and in the ileum. The organism was apparently avirulent for guinea-pigs and mice. They grew much faster than human tubercle bacilli. Although the organism was not definitely identified, it is concluded that it must have been a tubercle bacillus of the avian type.

MAX PINNER.

THE PROBLEM OF BARTONELLA INFECTION OF RATS. E. LAUDA and F. MARCUS, Centralbl. f. Bakteriol. **107**:104, 1928.

The authors discuss the problem as to the nature of the virus concerned in the infectious anemia of rats, and conclude from their experiments in which various drugs causing hemolysis were used that the so-called *Bartonella* bodies are not degeneration products but are probably organisms as claimed by M. Mayer.

PAUL R. CANNON.

THE MECHANISM OF TRICHINA INFECTION. JULIAN H. LEWIS, Centralbl. f. Bakteriol. **107**:114, 1928.

Lewis shows that the poorer muscles are in glycogen the greater the invasion by *Trichinae*. Guinea-pigs injected frequently with insulin and then infected showed a much heavier infestation with *Trichinae* than did the normal controls. Conversely, dextrose feeding of such animals favored a lighter infestation. The author believes that the organotherapy of *Trichinae* is best explained by some chemotactic substance resulting from the catabolism of glycogen.

PAUL R. CANNON.

THE REACTION OF VARIOLA VACCINE-VIRUS IN TISSUE CULTURE. E. HAAGEN, Centralbl. f. Bakteriol. **109**:31, 1928.

Vaccine virus in rabbit-testis tissue culture developed well provided it was freshly explanted every four or five days. The virulence of the virus cultivated in this manner for eight months through thirty-seven passages remained for the most part unchanged, and in a few cases, even, increased.

PAUL R. CANNON.

THE INFLUENCE OF JENSEN SARCOMA ON THE INFECTIOUS ANEMIA OF RATS. W. KIKUTH, Centralbl. f. Bakteriol. **109**:51, 1928.

Kikuth attempted to confirm the observations of Hirschfeld and Tinozzi that, in rats in which Jensen sarcomas were implanted, splenectomy led to less serious effects from the development of *Bartonella* anemia. The latter observers suggested that the tumors either secreted protective substances against the agent of the

anemia, or stimulated the reticulo-endothelial system in some manner. Nine rats were injected with Jensen sarcoma and later splenectomized. Nine normal rats served as controls. All of the rats with tumor developed *Bartonella* anemia, although the death rate was not so rapid as in the controls. Kikuth concluded that the somewhat less marked susceptibility of the rats injected with sarcoma to the development of the anemia following splenectomy is best explained by the fact that in these animals there is more stimulation of the bone marrow and more blood regeneration than in normal animals. As a result, the development of the bartonella virus is somewhat restrained.

PAUL R. CANNON.

THE RÔLE OF BED-BUGS (CIMEX LECTULARIUS) AND TICKS (ORNITHODORUS MOUBATA) IN THE TRANSMISSION OF ANTHRAX. H. P. ROSENHOLZ and O. W. OWSJANNIKOWA, Centralbl. f. Bakteriol **110**:160, 1929.

The bite of bed bugs and ticks which had been infected with anthrax bacilli caused no infection in white mice. In some insects, however, anthrax infection persisted in the gastro-intestinal tract for as long as one month. The feeding of such insects with blood from anthrax-sick animals led to the passage of anthrax bacilli into the body cavity where the organisms multiplied. In the dead bodies of such insects the anthrax bacilli remained alive for as long as six months.

PAUL R. CANNON.

HYDROGEN ION CONCENTRATION IN THE BLOOD OF TUBERCULOUS RABBITS. H. ZAIN, Ztschr. f. Tuberk. **53**:215, 1929.

The p_H values in the blood of tuberculous rabbits are within the limits of normal variation. This is true for both slightly and severely diseased animals. Only occasionally are values found which are slightly below the normal.

MAX PINNER.

END-RESULTS IN METAL SALT THERAPY IN TUBERCULOSIS IN RABBITS. L. E. WALBUM, Ztschr. f. Tuberk. **53**:292, 1929.

In all these experiments which cover a period from 1925 to 1929, rabbits were infected with 0.0001 mg. of bovine bacilli intravenously. The treatment with the various salts was started thirty-three days after the infection, that is at a period at which the tuberculous disease was fairly well advanced. Forty-two different metals were examined, but only two were found namely, cadmium and manganese, which had a definite and specific therapeutic action. Eight other ones (cerium, barium, aluminum, lanthan, molybdene, platinum, nickel and samarium) had a weak therapeutic action. All the other ones remained without influence on the development of tuberculosis.

MAX PINNER.

THE FATE OF B.C.G. IN THE ORGANISM. W. A. LUBARSKI, Ztschr. f. Tuberk. **53**:427, 1929.

After the injection of 5 mg. of B.C.G. into guinea-pigs, acid-fast organisms could be demonstrated for from six to eight months. Bacteriolysis was not observed. The organisms disappear after decomposing into granules and by excretion through the intestinal canal. This indicates that revaccination in children should be done after one year.

MAX PINNER.

THE RESISTANCE OF TUBERCLE BACILLI AGAINST EXTERNAL INJURIES. R. BIELING, Ztschr. f. Tuberk. **53**:512, 1929.

A rather dense but homogenous suspension of tubercle bacilli was kept in water of 70 degrees for one-half hour, and was kept twice in boiling water for one-half hour; then 0.5 per cent phenol was added. Five guinea-pigs received 1 cc. sub-

cutaneously on three successive days. One of these five guinea-pigs developed tuberculin allergy and was killed ten weeks after the injection. Its lymph glands were much enlarged but not caseated. Tubercle bacilli could not be demonstrated in the glands. Two other guinea-pigs were injected with the lymph glands and the spleen of the first animal. The animal injected with the material from the lymph glands developed generalized tuberculosis. In a second experiment, it was found that some tubercle bacilli remained alive, although with much lowered virulence, after the following treatment: Broth cultures were kept fifteen minutes in the autoclave at 102 degrees. After this, they were heated to from 70 to 80 degrees for at least six hours. The bacillary mass was filtered off and kept in 70 per cent alcohol for several months. These experiments would indicate a much higher degree of resistance in tubercle bacilli than that usually reported, and they show the importance of testing more than one animal, in order to prove the effectiveness of sterilization procedures.

MAX PINNER.

FUNGI AS THE CAUSE OF ABORTION IN CATTLE. H. C. BENDIXEN and N. PLUM, Acta path. et microbiol. Scandinav. **6**:252, 1929.

Seventeen cases of abortion in cows were studied and cultures made from the placentae. *Aspergillus fumigatus* was isolated in eight cases, *Absidia ramosa* in two cases and both organisms in the remaining seven. When both organisms were isolated, it is highly probable that only one was the causative agent and that the other was present as the result of contamination after birth. Microscopically, the hyphae were found in the placental tissue where they had caused widespread necrosis and considerable exudation. Macroscopically the cotyledons were composed of a yellowish-gray or brownish necrotic tissue, which is characteristic of the disease. Five pregnant cows were injected intravenously with the spores or conidia of the organisms, and in all cases the same pathologic changes occurred in the placentae as were found following the natural disease.

Immunology

EXPERIMENTAL PERITONITIS AND PERITONEAL IMMUNITY. S. F. HERRMANN, Arch. Surg. **18**:2202, 1929.

The author conducted several experiments in an attempt to produce a peritoneal immunity to infection, chiefly of *B. coli* and of streptococci. Intraperitoneal injection of colon bacilli was carried out, and some degree of resistance to infection from feces was obtained. Intraperitoneal injection of a vaccine of streptococci and colon bacilli was also carried out, mainly on rabbits, and 80 per cent of the rabbits so immunized survived infection from fecal soiling of the peritoneal cavity. It was seen that the protection was due to local immunization, because rabbits injected with the same vaccine subcutaneously were not so protected. The author was able to show a high degree of positive blood cultures in rabbits dying of peritonitis. There was a much higher number of positive blood cultures in those in which peritonitis did not develop after soiling of the peritoneal cavity by fecal contents, indicating that the reaction of the peritoneum, or in other words, the development of peritonitis, constitutes a local defense mechanism.

N. ENZER.

THE EFFECT OF REPEATED INJECTIONS OF EPINEPHRINE ON THE HEMOLYSIN FORMATION IN SUPRARENALECTOMIZED RATS. DAVID PERLA and J. MARMORSTON-GOTTESMAN, J. Exper. Med. **50**:87, 1929.

Epinephrine diluted with physiologic salt solution or with isotonic dextrose solutions and injected in amounts of 0.2 mg. per kilogram of body weight twice daily into suprarenalectomized rats raises their antibody-forming capacity. This result is not entirely dependent on the effect of the diluting fluid.

AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES IN RELATION TO THE SUPRARENAL GLAND. J. MARMORSTON-GOTTESMAN and DAVID PERLA, J. Exper. Med. **50**:93, 1929.

Suprarenalectomy is followed by a disturbance in the antibody-forming mechanism of the body. The suprarenal gland plays a rôle in the water metabolism of the tissues. Restoration of the water exchange in the tissues to a normal level is sufficient to raise the antibody-forming capacity to normal.

AUTHORS' SUMMARY.

THE PRODUCTION AND TITRATION OF POTENT HORSE ANTIPNEUMOTOXIN. JULIA T. PARKER and MARY VAN S. MCCOY, J. Exper. Med. **50**:103, 1929.

The serum of horses immunized with increasing doses of certain anaerobically produced autolysates of pneumococci contain potent neutralizing antibodies for the pneumotoxin. The method for the in vitro titration of these horse antipneumotoxic serums is given.

AUTHORS' SUMMARY.

EFFECT OF ANTI-AUTOLYSATE SERA ON PNEUMOCOCCUS PNEUMONIA IN GUINEA PIGS. JULIA T. PARKER, J. Exper. Med. **50**:161, 1929.

Antipneumotoxic serums prepared in rabbits or horses by immunization with sterile filtrates of the pneumotoxin, under certain conditions protect against the pneumonia caused by the intratracheal injections of mixtures of living pneumococci and toxic autolysates. The protection against the development of pneumonia is heterologous, at least as regards type I. Type 2, an anti-autolysate serum prepared by the immunization with a pneumotoxin from one type of pneumococcus will prevent the development of pneumonia caused by the injection of pneumococci and autolysate from another type. Certain antipneumococcus horse serums used in the treatment of pneumonia in man, contain either no heterologous pneumonia-preventing antibodies or slight amounts only. These serums, however, protect against the pneumonia produced by injections of pneumococci and pneumotoxin of the homologous strain, the degree of protection depending on the amount of specific protective substances such serums contain. Antipneumotoxic serums produced in rabbits or horses by the injection of sterile Berkefeld filtrates of the toxic autolysates contain no pneumococcus specific protective substances.

AUTHOR'S SUMMARY.

RELATION OF VACCINAL IMMUNITY TO THE PERSISTENCE OF THE VIRUS IN RABBITS. PETER K. OLITSKY and PERRIN H. LONG, J. Exper. Med. **50**:263, 1929.

By means of cataphoresis vaccine virus can be obtained from suspensions of tissue which are inactive by the usual tests of animal inoculation. Active virus can be obtained by cataphoresis from the tissues of rabbits long recovered from the effects of cutaneous vaccination. Evidence is brought forward which suggests that immunity in a virus disease, such as vaccinia, may be linked with the persistence in the body of living virus.

AUTHORS' SUMMARY.

THE REMOVAL OF AGGLUTININ FROM SENSITIZED MOTILE BACTERIA. JOHN B. NELSON, J. Exper. Med. **50**:377, 1929.

The salt-free water washings of a sensitized motile bacterium (*B. aertrycke*) were found to cause a floccular agglutination in the presence of both whole and deflagellated antigen. Evidence was presented that the water washings when salt-free contained flagella and flagellar agglutinin and that clumping occurred on the addition of saline. The floccular reaction in the presence of deflagellated bacteria was regarded as the agglutination of flagella present in the washings. In the presence of whole bacteria, however, actual bacterial agglutination resulted.

AUTHOR'S SUMMARY.

ON ISOAGGLUTININ REACTIONS OF HUMAN BLOOD OTHER THAN THOSE DEFINING THE BLOOD GROUPS. K. LANDSTEINER and PHILIP LEVINE, J. Immunol. **17**:1, 1929.

A study was undertaken on the occurrence of atypical iso-agglutinin reactions of human blood. Such a technic was purposely chosen as would detect serums of even slight activity. In this way rather numerous irregular reactions were found in a material obtained from patients with mental diseases. Most of the reactions observed may be put under the heading of cold agglutination, that is, the serums are active only at low temperature and give weak agglutination at room temperature (20 degrees). A smaller number of serums (about 3 per cent) contained agglutinins of a type intermediate between cold agglutinins and typical iso-agglutinins since their reactions were distinctly noticeable also under the usual conditions of blood grouping. In all of the cases with atypically reacting serums the blood cells showed no abnormal behavior and could readily be grouped. Also the grouping of the serums was not interefered with by the presence of the irregular agglutinins. Hence the irregularities are superimposed on the much more prominent group properties, and are not in conflict with the scheme of the four blood groups, the usefulness of which cannot be questioned (Thomsen). With regard to the practice of transfusions, it may be stated that in several instances in which the serum of the recipient contained irregular agglutinins for the blood of the donor no untoward symptoms were observed. Several serums of groups O, A and B, described, had agglutinins which were similar with regard to their specificity. In groups A and AB two types of agglutinins were found specific in general for cells of one or the other subgroup of group A; those agglutinating blood AA^2 showed in addition a specific action on cells of group O (Schiff). The properties of these serums demonstrate again definitely the existence of subgroups in group A, a distinction hardly significant at present for practical purposes. The results with the abnormal agglutinins of human serums give further support to the conclusion that there exists a great number of individual differences of human blood.

AUTHORS' SUMMARY.

THE SPECIFICITY OF MAMMALIAN SPERMATOZOA, WITH ESPECIAL REFERENCE TO ELECTROPHORESIS AS A MEANS OF SEROLOGICAL DIFFERENTIATION. STUART MUDD and EMILY B. H. MUDD, J. Immunol. **17**:39, 1929.

Spermatozoa of man, rat, guinea-pig, bull and ram injected into rabbits induce the production of antibodies which are species specific. Cross reactions occur between bull and ram spermatozoa and their corresponding antiserums. Inconclusive evidence is found of cross reaction between antiram sperm serums and guinea-pig spermatozoa. Electrophoresis, in spite of technical difficulties in working with spermatozoa, is found to be an adequate means of making these serologic differentiations. In confirmation of other investigators, antirabbit sperm antibodies have been induced by intravenous injection of rabbit spermatozoa into rabbits. Mammalian spermatozoa therefore possess both species and tissue specificity.

AUTHORS' SUMMARY.

THE REACTION OF THE WHITE BLOOD CELLS TO SPECIFIC PRECIPITATES. H. W. CROMWELL and J. A. CENTENO, J. Immunol. **17**:53, 1929.

When fresh normal citrated blood is mixed with a protein and its specific antibody, the polymorphonuclears, lymphocytes and mononuclears become strikingly vacuolated. This vacuolation is definitely associated with the product of the antigen-antibody reaction since it does not occur if the precipitate is removed before the whole blood is added, and the reaction does occur when the whole blood is added to the thoroughly washed precipitate suspension. Nonspecific particulate matter, as heat-coagulated protein, collodion particles and charcoal particles, does not stimulate the reaction. Phagocytosis of sensitized *B. typhosus*

and pneumococcus by the same types of cells has been observed with marked vacuolation of the polymorphonuclears and mononuclears. The vacuolation appears more slowly than with the specific precipitate and seems not to occur in the lymphocytes. It is considered that the specific precipitate is probably phagocytosed and that the vacuoles are associated in some manner with its subsequent digestion. These observations are significant in pointing out the probable importance of phagocytosis in determining the fate of the specific precipitate in vivo.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF BRUCELLA ABORTUS AGGLUTININS IN HUMAN SERUM. C. M. CARPENTER, RUTH BOAK and O. D. CHAPMAN, J. Immunol. **17**:65, 1929.

Agglutination tests for evidence of *B. abortus* infection on the serum collected from 4,050 Wassermann samples in Syracuse, N. Y., showed 7.3 per cent to contain abortus agglutinins. An examination of 955 similar samples of serum collected in New York City showed 2.4 per cent to agglutinate a *B. abortus* antigen. *B. abortus* agglutinins could not be demonstrated in the serum from adults who had been drinking pasteurized milk containing such antibodies. Evidence is submitted to indicate that *B. abortus* agglutinins in the blood serum are a result of an active production by the living organism which has invaded the tissues of the body. *B. abortus* agglutinins may disappear from human serums slowly. One serum titer was 1:405 two years after apparent recovery from undulant fever. Because of the variable antigenic properties of certain strains of *B. abortus*, no specific serum titer can be established as diagnostic of undulant fever.

AUTHORS' SUMMARY.

RELATIONSHIP OF SCHULTZ-CHARLTON REACTION AND SERUM DILUTION. MARGARET E. WYLIE, J. Infect. Dis. **45**:1, 1929.

The blanching power of a given serum is not directly proportionate to its dilution or concentration. With dilute solutions the results are unreliable, although positive results may occasionally be obtained. In practice it is inadvisable to use a dilution higher than 1:100. If the serum is diluted, it matters little whether the strength used is 1:10 or 1:100. The most accurate results are given by undiluted serum.

The time inverval between the initial injection and the appearance of blanching varies within wide limits, from one to forty-eight hours.

The Schultz-Charlton technic cannot be regarded as even a rough method of estimating the potency of a serum.

AUTHOR'S SUMMARY.

EFFECT OF HEATING SYPHILITIC SERUM AND ITS PROTEIN FRACTIONS ON PRECIPITATION REACTION. M. NISHIO, J. Infect. Dis. **45**:148, 1929.

Globulin from syphilitic serum, whether unheated or heated for thirty minutes at 56 C., gives precipitation results with the Kahn test, similar to those given by the same syphilitic serum after heating for thirty minutes at 56 C.

Unheated albumin from syphilitic serum prevents or reduces precipitation given by the globulin. This property is not manifested when the albumin is heated for thirty minutes at 56 C.

The protection to precipitation exerted by unheated albumin appears to be an inverse function of the concentration of the reacting substances of the serum and antigen.

AUTHOR'S SUMMARY.

STUDIES IN ANTIRABIES IMMUNIZATION. G. STUART and K. S. KRIKORIAN, J. Hyg. **29**:1, 1929.

Statistical evidence and animal experiment have alike proved carbolized killed antirabies vaccine to be of undoubted efficacy in both pre-infectional and

postinfectional treatment. Statistical evidence is furnished by the results of treatment of 90,000 patients, while experimental proof rests partly on the resistance shown by immunized animals to artificial infections with street virus, and partly on an estimation of degree and duration of rabicidal properties in their serums.

The Bordet-Gengou reaction is of no value as a qualitative or quantitative test for the estimation of antirabies immunity.

The efficacy of killed carbolized vaccine and probably of other antirabies vaccines is largely dependent on the concentration of the dosage and the period within which it is administered. Better results follow the giving of small doses over a number of days than the giving of larger doses over a shorter period.

It is impossible to reduce below a certain limit the time over which the total quantity of vaccine ordinarily sufficient for complete immunization can be usefully administered.

The effect on rabbits of the subcutaneous injection of freshly fixed virus is dependent on the quantity of virus introduced and on the duration of its period of administration. Few inoculations are more likely to cause death than several; repeated inoculations ordinarily confer immunity. Immunity thus acquired must have been produced within eleven or twelve days.

AUTHORS' SUMMARY.

FATAL REACTION FROM TRANSFUSION OF BLOOD. L. J. WITTS, Lancet **1**:1297, 1929.

An instance is reported of death from "hemoglobin infarction of the kidneys" following transfusion. The preliminary test-grouping and cross-agglutination did not indicate any incompatibility on the part of donor and recipient.

INVESTIGATION CONCERNING THE BLOOD GROUPS OF HORSES. S. SCHERMER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **58**:130, 1928.

Iso-agglutinins were found which showed two different blood corpuscle and two corresponding serum properties. They occurred in four combinations. In 16 per cent of fifty horses examined the blood could not be placed in any of these groups. Their blood gave reactions which, with only two known factors, could not be worked out.

The agglutinins of horse blood are weak, and the author states that consequently it is not always possible to estimate the blood group of a horse. He also states that with the knowledge of blood groups race differences are determinable.

ROY C. AVERY.

THE TECHNIC OF THE RIECKENBERG-BRUSSIN REACTION. W. P. JAKIMOW, Ztschr. f. Immunitätsforsch. u. exper. Therap. **58**:413, 1928.

The adhesive power of the immune bodies is strengthened by addition of a drop of normal citrated blood. The serum of rats and rabbits immunized with killed cultures of *S. recurrentis,* exhibited the adhesion phenomenon, in like manner as the serum from animals that have recovered from infection. Plasma and serum from an animal infected with a strain contains immune bodies not only against that strain but also against the original strain. Antibodies (thrombocytobarin) producing the adhesion phenomenon can be transferred passively to healthy animals.

ROY C. AVERY.

THE FUNCTION OF THE RETICULO-ENDOTHELIAL SYSTEM IN CHEMOTHERAPEUTIC ACTION AND ITS INDEPENDENCE OF THE PROTECTIVE FUNCTION. I. L. KRITSCHEWSKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **59**:1, 1928.

An unrecognized function of the reticulo-endothelial system is described in earlier papers by the author and by Meersohn. This function determines the

curative action of chemical preparations and rests on the capacity of these cells to absorb the therapeutic agent and to release it gradually to the blood stream. In splenectomized animals, the chemotherapeutic effect is stronger if the arsenical preparation is used with 6 per cent agar instead of physiologic salt solution because the subcutaneously injected agar is supposedly similar in its action to the spleen, in that it absorbs the chemical preparation and only gradually releases it to the blood.

ROY C. AVERY.

IMMUNIZATION OF APES WITH B C G. F. GERLACH and R. KRAUS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **59**:306, 1929.

The subcutaneous injection of from thirty to fifty mg. of Bilie Calmette Guérin strain was tolerated well by apes without injury. The animals possessed an immunity against subsequent tuberculous infections of both the bovine and the human types. Seven control apes showed typical progressive tubercular lesions at the point of inoculation, while ten immune apes, treated subcutaneously with B C G were able to withstand a virulent infection and showed no lesions.

The authors believe not only that progressive tubercular lesions produced by virulent and pathogenic strains give rise to immunity against infection, as previously thought, but also that attenuated, tuberculogenic but not pathogenic bacilli which produce a local benign lesion can give rise to immunity against virulent strains of the human and bovine type.

ROY C. AVERY.

THE COMPLIMENT CONTENT IN SERUM OF GUINEA-PIGS FED ACID AND ALKALINE FOODSTUFFS. W. E. HILGERS and H. ZAIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **59**:517, 1928.

The compliment content in serum from guinea-pigs which are fed alkaline or acid diet in such a manner that they do not lose weight, shows no difference capable of proof when contrasted with normally fed animals of equal weight. In one case, lipemia developed in an animal fattened with oats which showed a diminution of compliment in its serum.

ROY C. AVERY.

A CRITIQUE OF THE HIRSZFELD HYPOTHESIS CONCERNING THE GENETIC RELATIONSHIPS BETWEEN BLOOD GROUP AND SCHICK REACTION. E. ROSING, Ztschr. f. Immunitätsforsch. u. exper. Therap. **59**:521, 1928.

The author has shown that there exists no genetic relationship between blood group and the Schick reactions of parents and children. Only twenty-three of fifty children showed a Schick reaction similar to that of the parent to whose blood group they belong, while the remaining twenty-seven were different. The results do not confirm Hirszfeld's observations.

ROY C. AVERY.

THE INTRA-OCULAR INFECTION OF RABBITS WITH B C G. N. FUJIOKA and A. FUCHS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **60**:121, 1929.

The authors have again shown that the B C G strain by intra-ocular infection in rabbits is biologically different from the virulent bovine type in that it produces a benign localized process, which shows a tendency to heal completely.

ROY C. AVERY.

MOUSE INFECTION WITH B C G AND TRANSMISSION TO GUINEA-PIGS. N. FUJIOKA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **60**:125, 1929.

Tubercle bacilli of the human, bovine and avian types and also the B C G strain could be cultivated from the organs of mice several months after peritoneal infection.

Organ emulsions of mice injected several months previously with human and bovine types were found to be infectious for guinea-pigs. The B C G strain could not be transmitted in this manner.

ROY C. AVERY.

HISTAMINE SUSCEPTIBILITY AND ANAPHYLACTIC REACTIONS. G. W. SCHMIDT and A. D. STAHELIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **60**:222, 1929.

The minimal dose of histamine chlorate was determined for guinea-pigs by different routes of injection. Intravenous injection proved the more effective mode of administration.

The symptomatology of acute histamine shock is always the same regardless of the route by which it is administered.

The histamine sensitiveness in animals generally parallels their susceptibility to anaphylactic reaction. The author believes the results for the most part contradict the theory that anaphylactic symptoms are produced through histamine or histamin-like substances.

ROY C. AVERY.

THE ACTIVATION OF FORSSMAN ANTIGENS. C. HALLAUER, Ztschr. f. Immuniäts-forsch. u. exper. Therap. **60**:293, 1929.

The author shows that the euglobulin or pseudoglobulin fraction of rabbit serum like the whole serum itself when mixed with horse kidney extract and injected into rabbits does not activate the Forssman antigen. Pig plasma functions as well as pig serum in the process of activation.

ROY C. AVERY.

SYPHILIS FROM BLOOD TRANSFUSION. J. FREUCHEN, Ugesk. f. Laeger **91**:386, 1929.

Three cases of syphilitic infection in the course of blood transfusion are cited. In one case the donor became infected. The cannula first used for the patient having been removed and then by mistake placed in the vein of the donor.

Tumors

ADENOMA OF THE COIL GLANDS. M. H. GOODMAN, Arch. Dermat. & Syph. **20**:10, 1929.

This is a report of an adenoma of the axillary sweat glands. The tumor occupied the position in the cutis where sweat glands are usually present. Normal coil gland structures were associated with the adenomatous and cystadenomatous elements. There was evidence of persisting function in some of the hyperplastic glandlike structures. The belief that the tumor arose from apocrine gland tissue rests on the demonstration of iron pigment in the cells by the Turnbull reaction in sections. The exocrine glands do not secrete iron.

FRANK M. COCHEMS.

PROPERTIES OF THE CAUSATIVE AGENT OF A CHICKEN TUMOR. F. DURAN-REYNALS and JAMES B. MURPHY, J. Exper. Med. **50**:315, 1929.

Ground muscle from susceptible chickens fixes in vitro in a proportion of instances the agent of the filtrable chicken tumor I, and in a lesser degree inactivates it, whereas the muscle from resistant animals, such as the rabbit and pigeon, is without effect. It is shown that the power of fixation of the chicken muscle is far greater than its inactivating properties. Brain and liver from the chicken, rabbit and pigeon seem devoid of any action on the agent. The desiccated chicken muscle tissue shares the properties of the fresh organ, and the process of desiccation does not release the agent from the inactive or slightly active mixture of fresh muscle and filtrate.

AUTHORS' SUMMARY.

ENDOMETRIOSIS IN UTERINE CORNUA. MARION DOUGLASS, Surg. Gynec. Obst. **49**:138, 1929.

Cornual adenomas of the uterus were found in five of twelve specimens. The patients had not undergone any previous pelvic operation. This contradicts the

postsalpingectomy theory of Sampson in which it is supposed that there is direct operative implantation of endometrial or tubal mucosa or regurgitation of menstrual blood through the fimbria of the tubes. The author agrees with Novak that the primitive celomic mesothelium is concerned in the histiogenesis of endometriomas and regards the regurgitation of menstrual blood as infrequent. The association of inflammation in these specimens may bear some relation to these glandlike structures of the uterus.

RICHARD A. LIFVENDAHL.

THYROID TUMORS OF THE OVARY. G. L. MOENCH, Surg. Gynec. Obst. **49**:150, 1929.

Although only fifty cases of this type of ovarian tumors are recorded in the literature, the author regards them as occurring more frequently than this in that of twenty-one dermoids there were six in which there was thyroid tissue. In the three discussed in this article they were all very large cystic new growths that were filled by clear, light yellow fluid. In the wall of the cysts were typical dermoid tumors that contained cystic thyroid tissue. Chemical examination of the fluid in the tumors showed that it was free from iodine, glycogen and pseudomucinous material. Therefore, he denies Bauer's assumption that cases of struma ovarii are really pseudomucinous cysts. In one patient, after the removal of the tumor, the cardiac rhythm became normal and the fine tremor of the fingers disappeared.

RICHARD A. LIFVENDAHL.

THE STAINING OF MALIGNANT TUMORS WITH TRYPAN BLUE. R. J. LUDFORD, Proc. Roy. Soc. **104B**:493, 1929.

Injections of trypan blue in sufficiently high concentration to bring about an intense staining of the fibroblasts and histiocytes of the connective tissues, do not result in a coloration of the actively growing sarcoma cells of tumor-bearing mice.

ARTHUR LOCKE.

THE MITOGENETIC RADIATION OF CANCER. M. KISLIAK-STATKOWITSCH, Ztschr. f. Krebsforsch. **29**:214, 1929.

That the mitogenetic radiation of cancerous tissue is not due to glycolysis the writer shows by the fact that it is manifested by necrotic tissue. In freshly removed material it is manifested by the cellular portions; after twenty-four hours' incubation the effect is transferred to the fluid portions. He ascribes its origin to proteolysis, which, since it is not inhibited by the addition of potassium cyanide, is of anaerobic character.

H. E. EGGERS.

THE MITOGENETIC RADIATION OF CANCER. A. GURWITSCH and L. GURWITSCH, Ztschr. f. Krebsforsch. **29**:220, 1929.

While the mitogenetic radiation of cancerous tissues is in all probability due in large part to proteolysis, it is probable that glycolysis plays a part in its development, since in fresh living tissue the effect is shown only in the presence of dextrose. Too little is as yet known of the phenomenon to warrant an opinion of its rôle in the biology of tumors.

H. E. EGGERS.

CARCINOMA OF THE BILE PASSAGES IN DISTOMIASIS OF CATS. H. J. M. HOOGLAND, Ztschr. f. Krebsforsch. **29**:239, 1929.

There are reported four cases of carcinoma of the bile tracts in cats infected with *Opistorchus felinum*, with a fifth case in which cancerous changes were found only on microscopic examination. Intermediate stages between the proliferative growth determined by the parasite and the cancerous growth were to be observed

in three of the cases. The author is inclined to explain the cancer-producing action of the parasite as due to the liberation of carcinogenetic intoxicants.

H. E. EGGERS.

EXPERIMENTALLY INDUCED HEPATIC CIRRHOSIS IN RABBITS. G. DOMAGK, Ztschr. f. Krebsforsch. **29**:302, 1929.

In six of ten rabbits a diffuse hepatic cirrhosis, apparently secondary to degenerative changes in the liver, followed continued application of coal tar to the ear. There was associated splenic atrophy. None of the animals developed true cancer.

H. E. EGGERS.

CECAL CARCINOMA IN A 14 YEAR OLD GIRL. D. M. CHAJUTIN, Ztschr. f. Krebsforsch. **29**:389, 1929.

A case of adenocarcinoma of the cecum in a girl, aged 14, is here reported. The diagnosis was made only on histologic examination of autopsy material; the clinical diagnosis was intestinal tuberculosis.

H. E. EGGERS.

Medicolegal Pathology

POISONOUS ACTION OF INHALED ETHYL BROMIDE ON GUINEA PIGS. C. P. WAITE and W. P. YANT, Pub. Health Rep., **43**:2276, 1928.

Acute hyperemia and edema of the lungs were produced with high concentration (18 per cent), the animals dying within twenty-four hours. With a concentration of from 0.32 to 2.4 per cent and exudate of plasma and a few red blood cells occurred in Bowman's capsules about the glomeruli and in the renal tubules. When the animals survived no serious damage was found in the lungs or kidneys.

E. R. LECOUNT.

DETERMINATION OF THE COEFFICIENT OF POISONING WITH CARBON MONOXIDE FROM DECOMPOSED BLOOD. C. SIMONIN, Ann. de méd. lég. **9**:11, 1929.

This coefficient is a measure of the degree of intoxication suggested by V. Balthazard and M. Nicloux (Coefficient d'empoisonnement dans l'intoxication mortelle oxycurbonique chez l'homme, Comp. rend. Acad. d. sc. **152**:1787, 1911). It is obtained by dividing the percentage of carbon monoxide per hundred cubic millimeters bound to hemoglobin in the blood under examination by the percentage such blood will contain per hundred cubic millimeters when the hemoglobin in it is saturated. In short, it is a way of stating just how near the hemoglobin of any particular person or other animal came to being saturated with carbon monoxide by that poisoning. The degree of saturation is sometimes quite high. For example, in four persons killed by this gas in a burning building the coefficient ran 0.77, 0.87, 0.89 and 0.85, respectively. In the case reported by Simonin, the coefficient was 0.77. The blood came from the body of a young man found dead in the cellar of a hotel in Strassburg. The gas came from a water heater. Because he was seen, so it was said, five minutes before, the landlord claimed that death must have been caused by natural causes. The body was examined sometime after death, and hydrogen and methane were found in the blood with the carbon monoxide; no disease was found.

E. R. LECOUNT.

HISTOLOGIC DOCIMASIA OF CARBONIZED LUNGS. J. OLBRYCHT, Ann. de méd. lég. **9**:48, 1929.

A mother put her illegitimate child into a stove when it was born and burned the body so that some parts were altogether and others partly destroyed. She said that it was premature and that she had miscarried. Measurements of the epiphyseal center of ossification of the femurs, however, proved that birth had

taken place at term. Many of the viscera had escaped the flames. The kidneys, liver and spleen were the proper size for birth at term. The lungs, charred outside for a depth of from 2 to 7 mm., were carefully studied to see whether the child was born alive. Control lungs of nineteen fetuses were used, some human, others bovine and some of infants born alive. These lungs were also burned to duplicate as closely as possible the conditions of the lungs of the body found in the stove. It was learned that heat produces a rarefaction of the outer parts of lungs which may easily lead to the error of believing that the spaces found are a result of live birth and breathing. Since the lungs are not distended in all their parts by breathing for some time after birth, it was learned that burning may destroy the parts distended by inspired air and leave other parts never yet ventilated so intact that a wrong conclusion, that the lungs are those of a stillborn child, is easily possible. Consequently, Olbrycht, whose work was at the Medicolegal Institute of the Jagellonian University in Cracow, is pessimistic about the value of studying such lungs microscopically.

E. R. LeCount.

Poisoning with White Hellebore. P. M. Wrobleysky, Ann. de méd. lég. **9**:57, 1929.

Stomach trouble is generally blamed for death among rustic and barbarous people when poisoning occurs from the empiric use of herbs to which they are still accustomed. In Caucasia and Ukrania parts of the white hellebore plant are eaten with asparagus, and to promote secretion from mucous membranes and obtain its sternutatory effect a powder from the drug is scattered about in dwellings. As an adulterant, it is employed to increase the value of inferior tobacco. It is said to cause purulent otitis media when used in the last two ways. In these countries, it is also used as a decoction from the root for chronic heart disease and to produce abortions. Cases are also reported of poisoning with white hellebore intentionally induced in order to simulate heart disease. Two deaths were investigated at the Medicolegal Institute in Kharkof (Charkow), Ukrania, where Wroblewsky is Chief. The victims were both women who had taken a secret remedy, the one for heart disease, the other to bring on abortion. Both women died on the day that they were poisoned. The alkaloids of veratrin were readily found, and extracts of the viscera produced characteristic pharmacologic reactions in frogs and rabbits.

E. R. LeCount.

Barbital Poisoning. P. Muller, Ann. de méd. lég. **9**:72, 1929.

Idiosyncrasy was the explanation offered for the severe poisoning, a coma for about twenty-four hours, following two doses of 0.75 Gm. of barbital taken four hours apart with suicidal intent. In discussing the report of Muller, Kohn-Abrest emphasized the danger of the preparations of barbarturic acid when taken by persons with renal or hepatic disease. He also urged that the patient's tolerance should be tested carefully before any of these hypnotics are prescribed in other than small doses. When renal disease is present, there is likely to be nausea and vomiting, and intolerance is indicated by an intoxication resembling that of alcohol.

E. R. LeCount.

New Laws in France Pertaining to Dead Human Bodies. Duvoir, Ann. de méd. lég. **9**:77, 1929.

A new decree was signed by the Minister of the Interior and of Labor in March, 1928. The Act is in seven sections and was enacted chiefly to bring into accord various regulations previously in force. Section 1 is concerned with burial; section 2 with the transportation of bodies, and supplementing previous regulations are matters pertaining to hygiene, the use of disinfectants and the hermetical sealing of caskets; section 3 deals with exhumations. The previous obligatory attendance of a physician is abolished. Section 4 pertains to cremation. Certificates are

required from the attending physician and from a physician who is also a public official, regarding the cause of death before cremation can be carried out. In case these are not obtained an inquiry concerning the cause of death starts automatically. No authorization for cremation can be given unless the cause for death is a natural one. Section 5 consists of regulations for embalming and for this also a certificate from a physician is required setting forth that death resulted from natural causes. The use of arsenic, mercury and lead in embalming fluids is forbidden, and the methods of embalming are prescribed. Section 6 states under what conditions postmortem examinations may be performed and casts and death masks made from dead bodies. The provisions of this part of the decree require an interval between death and postmortem examinations made in private homes and does not affect the considerable freedom with which such examinations are made in hospitals. This interval seems too long when compared with practices in some other countries. In Section 7 supervision of the proceedings carried out with dead bodies is provided for, representation at embalming and postmortem examinations to prevent crime being hidden by, for example, removal of the uterus of women dead from abortion, of organs injured by bullets, etc.

The decree as a whole is not concerned with postmortem examinations conducted under military regulations. Since the previous decree of February, 1842, the right of hospital authorities to proceed with postmortem examinations has been recognized, and efforts to continue this practice have enjoyed thorough cooperation of the municipal and other officials who have recognized the interests of public health and medical science in postmortem examinations.

E. R. LeCount.

The Significance of Tattoo Marks. Coureaud, Ann. de méd. lég. **9**:100, 1929.

A careful study was made of the different designs, inscriptions, etc., tattooed on 300 men serving as marines in the French navy, both recruits and volunteers. It was found that tattoo marks had undergone a change; former depictions of events in mythology or in some chimerical romance long entrenched in the affections of the people were no longer employed as heretofore. The former delicately executed and artistic representations in many colors were replaced by coarse work of a low order. Consequently former complicated classifications were replaced by grouping them into only two classes. The first group was made up of emblems useful solely for identification and consisted of representations of anchors, buoys and other objects with which the marines were occupied daily; also figures referring to events such as bombardments, battles, places visited ashore, a dragon for the Orient, an oasis with palms, etc., and with these there were often dates. The marks of this group were often small and many were located on the back of the hand between the metacarpal bones of the thumb and index finger.

A second and much larger group of tattooings was made up of a great variety of designs of much greater medicolegal value. They indicated questionable morality or were definite insignia of sexual perversion, of secret societies, communistic affiliations, rebellion against or hate of discipline, etc. The "jackies" decorated with marks of this sort usually possessed records of punishment for infractions of regulations, or for graver offenses.

E. R. LeCount.

Accident and Osteosarcoma. Quenée and Muller, Ann. de méd. lég. **9**:122, 1929.

A laborer unloading slag with a wagon fell about 9½ feet twisting his right knee but without any direct violence to the part. Swelling began almost at once and this was followed by pain and a thickening of the periosteum below the patella in the tibia where the terminal tendon of the muscularis quadriceps femoris is inserted. It was thought that the periosteum there possibly was torn when the accident occurred. The symptoms and disability continued until almost a year later when by incision osteosarcoma was recognized. The authors believe that the

conditions observed fulfil all those which were agreed at the Congress of Legal Medicine in France in 1925 should be met to predicate successfully causal relation between accident and tumor.

E. R. LeCount.

Prolonged Intrathoracic Residence of a Fragment of an Artillery Shell. Trenel, Ann. de méd. lég. **9**:125, 1929.

This account has the following unusual features: The foreign body was not found until seven years after the injury; repeated attacks of hemoptysis caused the incorrect diagnosis of pulmonary tuberculosis; an unsuccessful attempt was made to remove the fragment nine years after the wound was received; the piece of metal was still there close to the root of the right lung as late as August, 1927, and there had been many revisions of war pension due to changes of incapacity.

When the injury was received, it was not expected that the man would live. The soft tissues including most of the muscles about the right pectoral and scapular regions and right shoulder were either shot away or subsequently removed, and the right side of the trunk, right arm and thigh were also severely injured.

E. R. LeCount.

Accidental Poisoning with Hydrocyanic Acid Gas. E. Kohn-Abrest, Ann. de méd. lég. **9**:132, 1929.

Nine deaths are reported of persons who entered places still incompletely ventilated after hydrocyanic gas had been used as an insecticide. The bodies were examined at different times after death: one after four, five after eight, one after eleven and two after fifteen days had elapsed. No trace of the poison was found in two of the bodies, one of these persons had died four days and the other eight days previous to the examination. In the remaining seven, traces of the poison were found, but free hydrocyanic acid was found in only one body; examination was made eleven days after death. After disinfection with the gas, traces imperceptible to smell and nevertheless highly dangerous may remain. Its use should be surrounded with strict precautions and regulations.

E. R. LeCount.

Carbon Monoxide Poisoning in a Colliery. B. Weissberger, Wien. klin. Wchnschr. **40**:1605, 1927.

During about eleven months of the year 1925, illness of sixteen laborers in a coal mine was noted and great perplexity over its nature resulted because by daily analysis of the air in the mine no carbon monoxide was found. The symptoms were of two kinds, hemorrhages and trouble with the nervous system. They exhibited a great variety: the hemorrhages were in the subcutaneous tissues, retinas or stomach, not all of them in each patient, however. Likewise the nervous symptoms of headaches, monoplegias, hemiplegias, speech paralysis, cardiac neurosis, hyperesthesia, paresthesia and insomnia were met with in different laborers; increased blood pressure and general weakness were also observed.

Three of the sixteen died, and two postmortem examinations were obtained. In one body, there were multiple hemorrhages in the spinal cord and brain with considerable blood in the fourth ventricle; the man, aged 44, died rather soon after the onset of symptoms. The other body was that of a man, aged 29, whose illness lasted for about a year. Following eight or ten days of headaches, a right hemiplegia developed. When this stroke came on his blood pressure was 185. There is no mention of any prolonged somnolence or coma such as occurs with acute carbon monoxide poisoning, yet when he died about a year after the stroke, softenings were found in each globus pallidus.

These changes in the brain, perhaps more than any other evidence, led to the conjecture that the complaints of all sixteen were due to carbon monoxide. There had been an explosion in the mine in 1924, and it was thought that the

carbon monoxide from that was adsorbed by dust and subsequently poisoned the miners. No tests of the blood were made. All the miners wore gas masks.

E. R. LeCount.

Accidental Poisoning with Hydrocyanic Acid Gas. M. Kaiser, Wien. klin. Wchnschr. **41**:958, 1928.

Prussic acid gas is extensively used in Austria to kill insects in houses. It is successful. It kills roaches, lice, bed-bugs, moths, beetles, mites, etc., although some may require a second disinfection. Bedding, clothing, rugs, fur and other materials used in households may retain the gas by absorption. Consequently, if the disinfection is done in cold weather, it is necessary to warm such goods or the rooms containing them to drive off the gas.

Two deaths and the poisoning of eight others who recovered resulted from failure to take such measures when household equipment was moved after disinfection to new homes in the winter. The warmth of the bodies of those who were poisoned released the gas, so it is stated. Three other deaths in Austria from the use of this insecticide are also mentioned, all, however, in other ways. The total space disinfected in 1927 was equal to 196,373 cubic meters, or a region about 190 feet in each of its three dimensions.

E. R. LeCount.

Internal Lesions in Electrocution. P. Schneider, Wien. med. Wchnschr. **79**:53, 1929.

In a power plant a man was electrocuted by a current of 5,000 volts; he gave one cry, fell and was then apparently dead. For one hour attempts were made to resuscitate him and during this time spinal fluid was withdrawn. The fluid came away in a stream under a pressure estimated as equal to 300 c.mm. of water. At the postmortem examination made two days after death, a few small subendocardial hemorrhages, considerable epidural spinal hemorrhage about the needle wound and an edema of the brain were found, and these, with the conditions encountered when the spinal fluid was withdrawn, were altogether regarded as evidence that the heart had continued to beat for some time after the shock was received; consequently, death was explained by effects that the current had on the central nervous system. There is no mention of any microscopic examination. If this had been done and very marked alterations had been found in the myocardium, death under the conditions related might be explained by defective blood supply to higher nerve centers. The current entered the palm of the right hand and passed out the sole of the right foot.

E. R. LeCount.

A Thalamic Symptom-Complex from Formaldehyde Poisoning. A. Weger, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:370, 1927.

In Charwok (Kharkof), Ukrania, both formaldehyde and phenol escape as vapors in the manufacture of bakelite from a natural product "Rigilite." Practically all the employes were found affected by the formaldehyde gas with which the air was saturated in compartments they were required to enter or in which they remained for varying periods. The symptoms were a general malaise; increased susceptibility to temperature changes; dizziness and severe headaches; a difference in the temperature of the two lateral halves of the body; abnormalities of sweating; disturbances of the temperature of and sensation in the skin, of the two lateral halves of the body, and dysesthesia, algesia and hemialgesthesia.

No opportunity was had to examine the central nervous system, but it is suggested that these remarkable clinical manifestations were caused by disturbances in the optic thalami, hypothalami and especially the tuber cinerea. The left thalamus was more often involved than the right. Presumably these parts of the brain have special chemical relations with the poison or poisons which are not possessed by other parts. The investigators believe that formaldehyde is more

to blame than phenol. New investigations are promised, and building modifications to secure satisfactory ventilation and prevent future similar poisonings were instituted.

E. R. LeCount.

Technical

Silver Staining of the Skin and of Its Tumors. George F. Laidlaw, Am. J. Path. **5**:239, 1929.

Long known as a capricious staining substance, silver does not always deserve this reputation. Provided that certain conditions are fulfilled, silver staining becomes as simple and as certain as the staining of nuclei with hematoxylin; at least, this is true of the peripheral nervous system, of the skin and of the argyrophil reticula generally. The conditions are: suitable fixation, suitable mordanting and the use of silver solutions from ten to twenty times stronger than those in vogue. The fixative determines the result of the stain. When the silver worker has grasped this principle, half of his difficulties disappear. Differential silver staining might well be called differential fixation, for a given silver stain will produce different effects according to the fixative employed. This paper deals with the application of these principles to the skin and to tumors of the skin, the fixatives selected being Bouin's fluid and neutral formol. The resulting preparations are described separately, for these fixatives are not interchangeable.

Author's Summary.

Light as a Factor in the Impregnation of Brain Sections with the Ammoniacal Silver Salts. Nathan Chandler Foot, Am. J. Path. **5**:365, 1929.

Frozen sections of brain tissue should be shielded from light before and up to the time that they are impregnated with silver salts. Light inhibits the impregnation of the oligodendroglia and microglia with silver diamino carbonate and produces troublesome precipitates in the sections. It does not appear to influence the impregnation of the macroglia materially. It somewhat inhibits the impregnation of the cortical neurons with silver diamino hydroxide, after bromuration. This fact may be made use of by technicians desiring to suppress these cells and their dendrites and to accentuate the microglia by contrast.

Author's Summary.

A Method for Securing Human Ova from Uterine Tubes. J. P. Pratt, E. Allen, Q. U. Newell and L. J. Bland, J. A. M. A. **93**:834, 1929.

Two methods to obtain living ova were used: In the first method, when the tubes were not to be removed, the uterus was compressed by uterine elevating forceps applied just above the cervix. A small needle with a syringe attached was then introduced through the muscle into the cavity of the uterus. Salt solution was then injected into the cavity and allowed to run out through the tube. One tube was compressed with the fingers while the other was being washed. The fluid was collected as it ran out the fimbriated ends and was carefully searched for ova. This method is also useful to test the patency of the tubes.

In the second method, when the tubes were removed at operation they were first dissected free from the mesosalpinx. A small cannula was fixed in the fimbrinated end of each tube and then washed with physiologic solution of sodium chloride. The washings were then examined for ova. Freeing of the tube seemed necessary, as otherwise there might have been a kinking which would have interfered with successful washing. Five undoubted ova have been recovered by the methods described.

A Rapid Quantitative Precipitin Technic. Alan Boyden and Joseph G. Baier, Jr., J. Immunol. **17**:29, 1929.

The measurement of volume of precipitate in the precipitin reaction has been found to be fairly simple, rapid and reliable when Van Allen thrombocytocrits are used. The technic described is recommended for the serologic study of biologic relationships where more measurements and fewer family trees are needed.

Authors' Summary.

The Diagnosis of Necrosis of the Pancreas by Diastase Determinations of the Urine. J. Wohlgemuth, Klin. Wchnschr. **8**:1253, 1929.

Titration of the diastase of the urine in a buffer-soluble starch medium at p_H 7.2 has been helpful in determining necrosis of the pancreas in thirty-six of thirty-eight patients. The details of the procedure should be consulted in the original article.

Edwin F. Hirsch.

Society Transactions

LOS ANGELES PATHOLOGICAL SOCIETY

Regular Meeting, May 14, 1929

NEWTON EVANS, *President, in the Chair*

CARCINOMA OF THE FALLOPIAN TUBE. ROY W. HAMMACK.

The patient was a woman, aged 48, whose complaint dated from Dec. 26, 1926. While sitting quietly in a chair, she suddenly had a vaginal flow of bright red fluid. For seven months, she used at least three pads daily. She never had any pain or discomfort, nor was there any loss of weight. In fact, during this period she gained several pounds. The fluid after the first time was not bloody, but clear. When she entered the hospital, examination showed a uterus of normal size with no nodules. Apparently an adnexal mass was not noted; at least there was no notation of it on the patient's chart. When the cervix was dilated, the probe met with an obstruction 1 cm. from the cervical outlet, and a diagnosis of uterine fibroid was made. Laparatomy was done with a tentative diagnosis of "possible malignant growth of the body of the uterus," and this specimen was removed. The specimen is a fallopian tube and was removed intact. It looked like a hydrosalpinx, measuring 4.5 cm. at one end, tapering to a normal size at the uterine end. The surface was smooth. When the tube was opened, a small amount of bloody fluid escaped, and the lining of the cavity was as you see it—a large number of rather soft, friable, papillary masses.

The microscopic features, as exhibited by the sections shown, include papillary epithelial structures, the composing cells showing considerable irregularity and a few mitotic figures. The nuclei are hyperchromatic. There is practically no infiltration of the wall, which is thin. It seems to be definitely malignant, though it shows little evidence of infiltration.

PULMONARY EMBOLISM FOLLOWING HIBBS' FUSION OPERATION. ROY W. HAMMACK.

The history of this case briefly was that of a young man about 32 years of age. Last November, he was carrying a large block of ice, and on letting down the load hurt his back. The pain persisted, and x-ray studies showed what was called a "slight slipping of one of the lumbar vertebrae." On April 1, a Hibbs' fusion of the third, fourth and fifth lumbar vertebrae was done. This operation and the convalescence were apparently uneventful until April 19, when the patient had a rather sudden rise in pulse and temperature. Examination at that time showed some pulmonary physical signs which were interpreted as bronchopneumonia. From that time on, the patient had mild persistent pulmonary signs, until on May 5, after he had apparently been improving, he suddenly became cyanotic and dyspneic, and died within about twenty minutes. Autopsy showed bilateral pulmonary thrombosis with infarctions of the lungs. The site of the operation on the lower vertebrae was investigated, and nothing unusual was found there, there being no evidence of infection or thrombosis. It was a coroner's case. There were thrombi of different ages in the lung, presumably having their origin at the site of operation. No other origin of emboli could be demonstrated at autopsy. The first symptoms, which followed operation by about two and one-half weeks, were possibly due to the lodging of the first emboli.

BUERGER'S DISEASE. REPORT OF A CASE. ROY W. HAMMACK.

The patient, a man aged 45, thought that he had injured his leg. The first evidence of trouble was a hard nodule in the course of one of the veins in his leg in July, 1928. Later, another lump appeared in another vein. It was evidently a migratory phlebitis, a rather characteristic sign of Buerger's disease. The phlebitis progressed and the patient entered the hospital in September. At that time, he had some slight discoloration and a little tenderness in his toes. He did not have symptoms of occlusion, except that he had a little pain in the right and left calf muscles when he walked any considerable distance. A tentative diagnosis of Buerger's disease was made and a piece of thrombosed vein was removed for microscopic examination. A thrombophlebitis, fairly characteristic of the disease, was demonstrated. In April, the patient's toes began to become discolored, with more marked pain. He received one intravenous injection of typhoid vaccine, and subsequently a number of injections of salt solution and Ringer's solution, but without any effect. His circulation became rapidly poorer, resulting in gangrene of the great toe. In spite of no visible evidence of disease of the leg other than an absence of pulsation of the arteries, a high amputation of the leg was done. The popliteal artery was found occluded at the point of amputation. Gangrene of the great toe and a gangrenous spot at the base of the fourth toe was observed on the amputated member.

The sections of the vein secured at biopsy were fairly characteristic. They showed an inflammatory lesion of the vessel wall with a thrombus in varying states of organization, with considerable round cell and some leukocytic infiltration. The presence of giant cells seemed rather characteristic. The lesion in the bit of vein removed before amputation seemed to be sufficiently characteristic to make certain diagnosis of obliterating thrombophlebitis, or Buerger's disease. Microscopic section showed fibrin in the center with more or less necrosis, and at the edge of the fibrin there were many infiltrating round cells. There was a beginning canalization, and in one of the sections at the margin of the fibrin among the round cells there were one or two giant cells. Throughout the wall of the vessel there were a good many round cells and occasional leukocytes.

The popliteal artery from the leg showed the wrinkled remainder of the lining of the vessel. There was a little area of calcification in the wall, but the whole lumen was filled with an organized thrombus, and canalization of the thrombus had taken place. Near the center of the thrombus there were brown areas of blood pigment. The irregular intima was well preserved. As Buerger claimed, it seemed to be a thrombotic process followed by the organization of the thrombus and finally more or less recanalization. It is accompanied by more or less acute inflammation.

RUPTURED PAPILLARY MUSCLE OF THE HEART. R. M. CRUMRINE.

The patient was a white man, aged 51. He was sent into the hospital with a diagnosis of "acute abdomen." On the day before admission, he had driven 60 miles in a car and had become very ill thereafter with pain which originated behind the sternum and radiated toward the umbilicus, and which was relieved by frequent vomiting. There was no pain in the shoulders or the arms. He had had similar abdominal pain two weeks before, and this had persisted more or less ever since. The patient was a cement worker, and his past health had been good.

He was admitted as having an acute abdominal condition, and a surgical consultant was called. The latter, however, diagnosed it as "acute cardiac failure, probably due to coronary disease." The surgical resident who made this diagnosis stated that the liver was enlarged almost to the umbilicus and was tender. He believed it to be a plain case of cardiac failure with cyanosis of rather peculiar distribution, involving only the head and shoulders. The heart sounds were distant, and a systolic apical murmur was present. Several attempts to obtain the blood pressure were unsuccessful. The patient died thirty-six hours after admission,

and at autopsy the abdominal cavity showed no peritonitis or other evidence of acute abdominal disease. The liver weighed 2,300 Gm., and the cut surface showed a definite nutmeg appearance. The heart weighed 450 Gm. and presented a complete rupture of one of the larger papillary muscles of the mitral valve. The torn surfaces showed considerable pinkish exudate. The coronary arteries were both markedly sclerosed, and there were large areas of fibrosis visible in the wall of the left ventricle. The aortic valve was normal, and the entire aorta showed only slight atheroma. Microscopic sections substantiated the opinion that the muscle was ruptured at a time probably two or three days before death. They also showed marked fibrous scarring of the papillary muscle and in the ventricular wall.

It is usually stated that ruptures follow acute or chronic occlusion of the left coronary, which is the sole blood supply of one of the papillary muscles of the mitral valve. Occlusion of other branches of the coronaries doubtless would contribute to fibrosis and rupture of other papillary muscles.

HEMORRHAGE INTO THE SUPRARENAL GLAND IN AN INFANT. R. M. CRUMRINE.

A 22 days old infant had hemorrhagic disease of the new-born and infection of the umbilical cord. The condition cleared up after one or two intramuscular injections of whole blood, but a peritonitis developed secondary to the infection in the umbilical cord. A mass was palpated in the right upper quadrant.

At autopsy, a resolving peritonitis was found. The mass in the right upper quadrant proved to be a hemorrhage into the suprarenal gland. The gland was nearly as large as a prune with hemorrhage extending under the renal capsule and forming a small mass at the lower pole of the kidney. The opposite kidney and suprarenal gland were normal. Microscopic sections showed a normal suprarenal cortex with hemorrhage into the medullary portion, a picture suggestive of infarction.

The temperature in this case was not extremely elevated, as is the case usually. The highest recorded temperature was 103 F.

TOXIC HEMORRHAGIC HEPATITIS. REPORT OF CASE. HOWARD A. BALL.

A male child, 21 months of age, for ten months had had a chronic skin condition, diagnosed as eczema. The child entered the hospital with an infection of the upper part of the respiratory tract, which had been present for about one week. Until this time, he had been considered by his mother to be perfectly well. He was a full term child and was instrumentally delivered; he was never breast fed.

Examination revealed that the face was covered with crusting lesions and that there was a similar condition of the skin of the body. Roughened breadth sounds and râles throughout the lungs were the only other positive observations. A white blood cell count was 10,300 per cubic millimeter, with a differential count of 80 per cent polymorphonuclear and 20 per cent mononuclear cells. The blood Wassermann reaction and the urinalysis were negative. There was no roentgenographic evidence of bronchopneumonia.

The child's general condition was considered good until five days after admission. The skin lesions on the body had completely healed. The child suddenly became ill and had what was described as a "waxy pallor." At this time, the red blood cell count was found to be 3,000,000, and the hemoglobin 50 per cent (Tallquist), few platelets being found in the smear. Because of the evident anemia and the weakened condition of the patient, a transfusion was proposed. The child succumbed before it could be started.

Examination of the body fifteen hours post mortem revealed a well developed and well nourished male child, with a stated age of 1 year and 9 months. Over the face were numerous pitted, granulating areas, some of which were round and punched out and others confluent, giving a serpiginous outline. Anterior to the right ear was an area of exuding skin; a similar area was present on the

anterior aspect of the neck. There were also a few punched-out areas on the right wrist and one on the extensor surface of the left forearm. Within the areas of postmortem livor could be seen darker colored patches of scaly skin, slightly raised above the surrounding surface. The lungs and heart showed no evidence of pathologic change.

The liver was large and markedly softened, and beneath the capsule could be seen mottled areas of yellow and red, somewhat simulating a patchy ecchymosis.

Fig. 1.—Gross appearance of cut surface of liver, showing numerous hemorrhagic areas, resembling a diffuse cavernous hemangioma. Microscopic examination reveals a liver necrosis and extensive areas of hemorrhage.

Cut section revealed throughout the entire liver substance areas of hemorrhage, not definitely circumscribed, some of which were firm and appeared as thromboses, the whole picture roughly resembling a large and diffuse cavernous hemangioma. Less than one third of the liver substance was uninvolved. The tissue was friable.

The spleen was small and somewhat mottled, its cut section not showing any prominent malpighian corpuscles. The kidneys were normal in size and were

definitely anemic. The cortex showed some cloudy swelling, and a slight icteric tinge. The bladder was normal. The mesenteric lymph nodes were swollen, but the intestine was without gross evidence of pathologic change. The bone-marrow showed no gross change.

Smears from the lesion anterior to the right ear showed numerous gram-positive cocci arranged as staphylococci. Smears from the liver showed no organisms, but much fibin and cellular debris.

Microscopic sections of the skin lesions showed a picture consistent with impetigo; gram-positive cocci were demonstrated at the base of the ulcerated area. Sections of mesenteric lymph nodes showed congestion, but no hemorrhage; and Gram-Weigert stains revealed no organisms. Sections of the liver (fig. 2) showed large and small areas of fibrin, within which were enmeshed many red and white blood cells in apparently normal proportions. Areas of early necrosis of the liver substance were present. Gram-Weigert stains revealed no organisms. Sections of spleen showed a tendency to formation of hemorrhagic

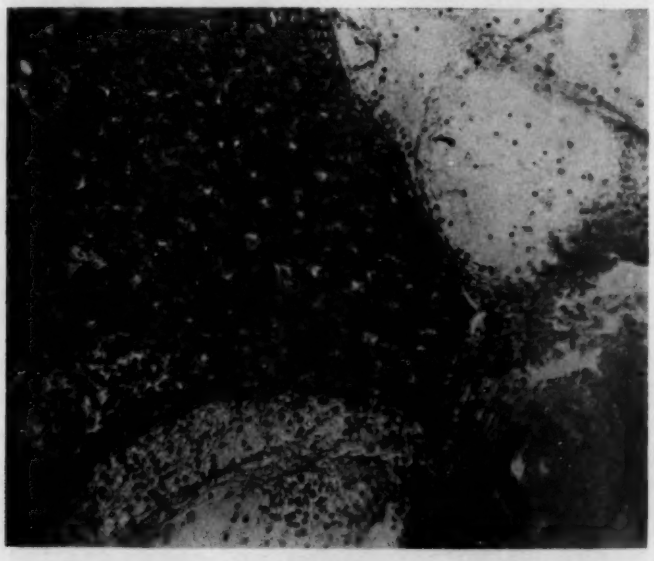

Fig. 2.—Photomicrograph showing areas of fibrin and enmeshed blood cells, and at the left, normal-appearing liver substance.

areas, being in this respect somewhat similar to the liver. Smears of the bone-marrow stained with Wright's stain showed no recognizable abnormality.

For want of a term more suitable we have called this toxic hemorrhagic hepatitis, cause undetermined. Whether or not it is an expression of a purpuric tendency, I am not prepared to say.

PRIMARY CARCINOMA OF LIVER, WITH FATAL HEMORRHAGE THROUGH THE COMMON BILE DUCT. HOWARD A. BALL.

This case of primary carcinoma of the liver is rather unique because of the mode of death.

A Mexican, aged 47, who had complained of "indigestion" for many years, entered the hospital, Jan. 22, 1929, with the complaint of bleeding from the stomach of two days' duration. The first blood vomited was bright red, and that of the next day was of coffee ground character.

Examination showed a patient in rather poor condition. The pulse was weak, the rate 80 per minute. The blood pressure was 100 systolic and 55 diastolic. The results of the examination were otherwise unimportant. The urinalysis showed nothing of note. The blood count showed 3,610,000 red blood cells per cubic millimeter, with hemoglobin (Sahli) 70 per cent; white cells 9,800 per cubic millimeter, with polymorphonuclears 79 per cent and mononuclears 21 per cent. A diagnosis of bleeding peptic ulcer was made, and the patient was given a transfusion of 450 cc. whole blood of the same type after a cross-agglutination test was negative. The patient died eighteen hours after entrance.

Autopsy was performed twelve hours after death. The only observations of note were in the liver and gastro-intestinal tract. The liver was of average size, but nodular over the surface, individual nodules averaging about 7 mm. in diameter, the typical picture of atrophic cirrhosis. There was fibrosis surrounding these nodular areas, and some variation in color, the major portion of the liver having the usual brownish color; but situated on the anterosuperior surface of the liver on the right side was a raised area measuring 8 by 8 cm., which was less nodular and light gray to yellow, and which was friable. This was later proved to be carcinomatous tissue. Situated in the porta, just above the junction of the cystic and hepatic ducts, was a necrotic mass of tissue, soft and fluctuant, which was found on gross section to consist of necrotic tissue with fluid and clotted blood. One hepatic duct was found connecting with this necrotic mass. This, as well as the common bile duct, contained necrotic tissue and clotted blood. The stomach and the small intestine contained at least a liter and a half (1,500 cc.) of partially digested bloody fluid, and it seemed evident that death was due to hemorrhage through the common bile duct. No esophageal or pyloric varices were present.

Cut section of the liver revealed tumor thrombi in many branches of the portal vein, but the exact point of communication between the portal system and the necrotic mass described was not demonstrated.

Microscopic sections of liver showed an active interstitial hepatitis, with numerous small round cells in the connective tissue, and a primary carcinoma of the liver cell type.

Fox and Bartels in a review of the English literature published since 1901 (ARCHIVES OF PATHOLOGY, August, 1928), collected eighty reports of cases of primary carcinoma of the liver, but made little note of the almost constant association with atrophic cirrhosis.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 10, 1929

J. HAROLD AUSTIN, *Presiding*

ACTION OF WHOLE FRESH BLOOD ON PNEUMOCOCCI. MYER SOLIS-COHEN and RACHEL ASH.

The present studies continue work previously reported by Heist and Solis-Cohen in which a capillary tube method was used to investigate and measure the bactericidal properties of whole fresh blood. In the present work, virulent strains of pneumococci were implanted in human blood of known resistance to such organisms. By making frequent subcultures from such capillary clots to the surface of blood agar slants, an actual diminution in number of colonies could be demonstrated, thus adding weight to the theory that pneumococci are destroyed in such blood. In an attempt to dissociate the influence of leukocytes from that of plasma, we made microscopic studies on clots centrifugated before coagulation had taken place. We found that growth of pneumococci occurred in the plasma

layer of such centrifugated clots before organisms could be observed in the leukocytic layer or in the usual Heist smear. Inhibitory action of whole blood against pneumococci would thus seem to be dependent on the action of leukocytes. In a centrifugated clot seeded with large numbers of pneumococci, emigration into the plasma is inhibited; whereas when few organisms are present leukocytes are attracted to the area of growth.

INTERMUSCULAR LIPOMAS: REPORT OF THREE CASES. MOSES BEHREND.

Greater care should be taken in the classification of these tumors. The overlapping of the terms intramuscular and intermuscular should be avoided. This can be done by a stricter analysis of the anatomic arrangement of these tumors. Some grow between the muscles, while others originate in the muscle. All our cases were of the intermuscular variety, which are rather more common than the intramuscular type. In either case, these tumors are rare.

Pure lipomas only should be included and not those of fibrous and fatty type, as has been done by some authors.

Lipomas growing between or within the muscle may occur in any part of the body. They are usually found in the extremities, a common place being the region of the trapezius muscle.

The symptoms of lipomas are those of benign tumors, depending on the size and location.

The differential diagnosis is of some importance and is difficult to make. Lipomas may be mistaken for angiomas, sarcomas or muscle tuberculosis. An exploratory puncture withdrawing some fatty material will always confirm the diagnosis. Examination by means of the x-ray will help in separating sarcoma from lipoma. One specimen was received from the anatomic laboratory of the Jefferson Hospital, the first ever noted by Prof. J. Parsons Schaeffer in an experience covering twenty-five years. The lipoma was under the trapezius muscle. The other two specimens were obtained from patients in my service in the Jewish Hospital. In one case, in a colored man, the tumor was under the trapezius muscle, while in the second case, in a woman, the lipoma was beneath the rectus femoris muscle.

In all, 190 cases have been reported, exclusive of the cases mentioned in this synopsis.

This paper with complete bibliography is published in full in *The American Journal of Surgery*.

PRIMARY SQUAMOUS CELL CARCINOMA OF THE VAGINA IN PATIENT 16 YEARS OLD AND SIX MONTHS PREGNANT. LOUIS TUFT.

This paper will be published in full in a later issue.

THE NEW BUREAU FOR THE STUDY OF TUMORS. JOSEPH MCFARLAND.

An abstract of this paper has been published in the ARCHIVES (**8**:837 [Nov.] 1929).

DEMONSTRATION OF AN INSTRUMENT FOR DETERMINING THE COAGULATION TIME OF THE BLOOD. GEORGE M. DORRANCE.

This simplified method of obtaining the coagulation time of the blood was first introduced to the medical profession sixteen years ago by Dr. G. M. Dorrance.

The present improved instrument consists of a rectangular glass container measuring 6½ inches (16.5 cm.) in length, 1½ inches (3.8 cm.) in width and 4 inches (10.16 cm.) in height. A bakelite cover with eight openings through which seven glass rods and a thermometer are inserted completes the instrument.

The principle of the test is to determine how long a time must elapse for clotting to occur in a drop of blood placed on the end of a glass rod (at body temperature).

Technic.—The container is half filled with water at a temperature of 99 F.; the cover is replaced and the rods allowed to remain immersed for half a minute; the cover is removed; the rods dried and drawn upward so that when the cover is reapplied their tips are about one quarter of an inch (0.61 cm.) above the water.

The finger of the patient is prepared and given a smart prick with a needle; the first drop of blood is mopped away, then an even film of blood is placed on the tip of each rod, care being taken to avoid touching the skin with the rod or allowing blood to touch the sides of the rod. At stated intervals of time, the rods are immersed in the water, and the time when clotting begins and ends is noted by the character of the precipitate. When the rods have been immersed, the cover is removed and the type of clot can be seen by holding the rods to the light; the tips are next gently mopped off on a clean towel, and the texture and character of the clot examined.

In this instrument, the normal clotting time is between five and eight minutes.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Nov. 11, 1929

HENRY C. SWEANY, *President, in the Chair*

PRIMARY CARCINOMA OF THE LUNG FOLLOWING TRAUMA. H. GIDEON WELLS.

This article will be published in full in a later issue of the ARCHIVES.

DISCUSSION

EDWIN F. HIRSCH: The relation of trauma to malignant growths is noted especially well in the distal parts of the extremities where, for example, following a bruise, fibrosarcomas appear, such as Harbitz has described in the ARCHIVES OF PATHOLOGY.

THE EFFECT OF EXPERIMENTAL HYPERTHYROIDISM AND OF INANITION ON THE HEART, LIVER AND KIDNEYS. J. P. SIMONDS and W. W. BRANDES.

This article appears in full in this issue, p. 445.

DISCUSSION

GEORGES M. CURTIS: In view of the results obtained by Dr. Simonds and Dr. Brandes, it is of interest to recall the work of one of Asher's pupils. Rohrer (*Biochem. Ztschr.* **145**:154, 1924), using a modified Krogh microespirometer, studied the oxygen consumption of surviving tissues. He first determined the volume of oxygen consumed by weighed bits of muscle, liver and kidney taken from normal control white mice. Other mice were then fed thyroid extract and the determinations repeated. In the resulting hyperthyroid state, muscle consumed 24 per cent more oxygen, liver 23 per cent and kidney but 16 per cent more than the normal organ. The increase in oxygen consumption for the entire animal was not given. In white rats, this is about 37 per cent (Curtis: *Biochem. Ztschr.* **167**: 321, 1926). Feeding of thyroid extract increases the oxygen consumption of surviving organs in varying degrees. These results may throw some light on the varying weight loss of organs in experimental hyperthyroidism.

LEUKOPLAKIA OF THE STOMACH. HARRY A. SINGER.

This article will be published in full in a later issue of the ARCHIVES.

THE INFLUENCE OF BLOCKADE OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE FORMATION OF ANTIBODIES. PAUL R. CANNON, RAYMOND B. BAER, F. L. SULLIVAN and J. R. WEBSTER.

Metchnikoff's idea that antibodies are products of the parenteral ingestion and digestion of foreign substances by phagocytic cells, has received additional support within recent years as a result of the interest in the functions of the so-called reticulo-endothelial system. According to the hypothesis of Metchnikoff, if phagocytosis and intracellular digestion of foreign materials could be prevented, antibody formation would also be prevented. Blockade of the phagocytic cells would seem to furnish a good method for the elucidation of the problem, but the results of such experiments have been inconclusive, some investigators having found a decrease in antibody formation subsequent to the so-called blockade, some an increase and others no effect at all. A close analysis of their work, however, reveals the probable causes of these divergent observations.

It is obvious that the blockade by particulate matter of every reticulo-endothelial cell of the mammalian body would be extremely difficult, and, indeed, is probably impossible. Even if it were possible, the adaptive powers of the body would soon furnish more phagocytic cells, either by further regeneration, or by differentiation of forms previously inactive. It is useless to expect complete blockade. Nevertheless, it should be possible to eliminate a great number of the actively phagocytic cells by blockading methods and, if the hypothesis of Metchnikoff is correct, to obtain a corresponding decrease in antibody formation.

In testing this idea, however, the following conditions are essential:

1. A proper amount and kind of blocking material must be injected.
2. This injection should be continued throughout the experiment.
3. Both intravenous and intraperitoneal injections of the blocking material are necessary.
4. A sufficient number of animals to eliminate individual variation must be used.
5. A small dose of "test antigen" should be employed. Adequate blockade of the reticulo-endothelial system cannot be expected unless the first three of these conditions are observed; and the effects of the blockade on antibody formation cannot be clearcut unless the last two are recognized.

The experiments here described were performed with the aim in view, first, to block as many of the phagocytic cells of the body as possible, and second, and of equal importance, to keep blocked these and any other cells that might regenerate or differentiate into active forms. This can be successful only if frequent intravenous, as well as intraperitoneal, injections are made. In addition, a sufficient number of animals must be used to eliminate the factor of individual variation. Even with these prerequisites it is probable that the results, as far as antibody formation is concerned, will be obscured unless the proper dosage of "test antigen" is used. This was shown by Motohashi when he demonstrated that splenectomy in the rabbit is followed by a decrease in the liberation of antibody into the blood stream only when a small amount of antigen is injected.

Thirty rabbits in all were used. The blockading material was a suspension of from 4 per cent to 8 per cent of Higgins' india ink (white label bottle) in 0.85 per cent sodium chloride solution. This was injected two or three times a day, intravenously and intraperitoneally, in amounts ranging from 5 cc. to 25 cc. At the end of two weeks of such blocking procedures, 0.5 cc. of a 0.5 per cent suspension of sheep's red blood corpuscles, washed five times, was injected intravenously. The sheep's cells were always from fresh blood and were centrifugated at the same speed for the same period of time during the last washing. The rabbits in each series were selected so as to be of practically the same weight, and a constant amount of antigen was injected into each animal. At intervals of time the serums, inactivated at 56 C. for thirty minutes, were titrated in a system as follows: 0.2 cc. of a 1 to 4 dilution of pooled guinea-pig serum, 1 cc. of diluted serum and 0.5 cc. of a 2.5 per cent suspension of washed sheep's corpuscles in 0.85 per cent sodium chloride solution. The highest dilution of serum causing complete hemolysis in

one hour at 37 C. was taken as the titer. In series 1 and 2, the blockading procedures were discontinued at the time of injection of the "test antigen"; in series 3 and 4, they were continued until the end of the experiment.

The results of these experiments may be summarized as follows:

1. The liberation into the blood stream of hemolysins to sheep's red corpuscles following blockading procedures depends on the manner of administration of the blockading material and the amount of antigen injected. Repeated injections of suspensions of india ink, particularly intravenously, and continued after the injection of a small quantity of "test antigen," are followed by a significant decrease in the liberation of antibody into the blood stream, this liberation apparently varying inversely with the extent to which the phagocytic cells are blocked.

2. This decrease in output of antibody is independent of the individual variation of the animals, of loss of weight or of depression by fluids alone.

3. Evidence is presented that small amounts of blockading material stimulate the liberation of antibody, whereas large amounts tends to depress such a liberation.

4. These experiments offer additional evidence that antibodies, at least hemolysin, are formed by the phagocytic cells of the mesenchymal tissues.

The complete report is published in the *Journal of Immunology* (**17**:441 [Nov.] 1929).

TWO CASES OF MALIGNANT ULCERATIVE ENDOCARDITIS OF THE PULMONARY VALVE. W. W. BRANDES, M.D.

The first case is that of a white woman, 25 years of age, whose chief complaint was nausea, vomiting and fever. During the course of the disease, however, joint pain and temperature of the septic type developed, and a murmur was heard over the pulmonic area. After repeated negative results, a positive blood culture was obtained, a nongreen-producing, nonhemolyzing streptococcus growing only on blood mediums and under partial oxygen tension being isolated. Pregnancy had been diagnosed, but criminal abortion was denied. The patient died on the twenty-fourth day in the hospital. The postmortem examination demonstrated massive, irregular, friable vegetations on the pulmonary valves apparently completely occluding the orifice of the pulmonary artery, and similar, but somewhat small, vegetations scattered along the entire length of the posterior wall of the artery to the hilum of the left lung. Numerous emboli were present in the intrapulmonic branches of the pulmonary artery, and multiple hemorrhagic infarcts, but no abscess. Acute fibrinous pleurisy was present. The right side of the heart was markedly dilated. There was a necrotic ulcer at the level of the internal os of the uterus on the posterior wall and a ragged reddish-gray area in the fundic portion. A small amount of thin grayish exudate was present over the rectum and posterior surface of the uterus. The spleen was large and soft. There were numerous petechial hemorrhages and small pustules in the skin of the back.

Histologic preparations contained decidual tissues and chorionic villi in the fundic portion of the uterus.

Gram's stain of the tissues demonstrated gram-positive chain-forming organisms in the vegetations, lungs, spleen, liver, uterus and glomeruli of the kidneys.

The second case was that of a colored man, aged 43, who cut his right thumb on a tin can. The thumb was amputated on the day following the accident, but septicemia developed rapidly and death followed in ten days.

The postmortem examination demonstrated a vegetation 10 by 12 mm. on one leaflet of the pulmonary valve and an ulceration of the intima of the aorta with marginal vegetations 5 mm. from the valves. There were multiple septic infarcts in the right lung, acute fibrinous pericarditis and pleuritis, a generalized fibrinopurulent peritonitis and descending infection of the kidneys.

These cases were brought before the society because of the infrequency of purely pulmonary valve involvement, but chiefly because of the massive size of the vegetations and special bacteriologic features in the first case.

Book Reviews

DIE BIOLOGIE DER PERSON. EIN HANDBUCH DER ALLGEMEINEN UND SPEZIELLEN KONSTITUTIONSLEHRE. By T. BRUGSCH and F. H. LEWY. Numbers 9 to 14. Berlin: Urban & Schwarzenberg, 1929.

The recent issues of this work contain several contributions of special interest to the pathologist. M. de Crini devotes an extensive article to the question of the humoral constitution. His discussion is based on the conception that for the organs of the human body, and in particular for the central nervous system, the body fluids belong to the outer world as do the fluid mediums in which the low forms of animal life exist. Arnold Josefson's chapter on the personality and the endocrine glands does not cover the field as completely as it would seem desirable. The personality is intimately influenced by the inner secretory glands. There exists an undetermined optimum in the activity and internal relation of the endocrine glands which secures the greatest efficiency in the defense against internal and external injuries. It is the inner secretory system which, to a great extent, determines the personality, and disturbances in this system are of great significance especially during the years of development.

In the period of cellular pathology the supporting structures were greatly neglected. The modern conception of constitution has given to these structures a paramount importance, since it is through them that the habitus of the individual is fixed. K. H. Bauer succeeds well in illustrating the part played by the connecting substances in the different problems of constitutional pathology.

Much valuable information also can be obtained from R. Weber's study on the teeth. Then follow two detailed chapters on the intestinal tract by F. Fleischer and on the eye by J. Helbron. The reviewer can recommend especially the latter chapter, which contains much valuable material for both the pathologist and the pharmacologist. Much space is devoted to the question of the influence of the environment (R. Michels) and the climate (F. Giese) on the person.

It is, of course, difficult to define sharply what should be included in a system of the biology of the person. There are chapters of a philosophic and religious content, dealing with the person and the community in their relation to Catholicism (L. Bopp), evangelical christianity (C. Fabricius), Islam (H. H. Schaeder) and Judaism (S. B. Rabinkow). A. S. Steinberg discusses the person in old and new Russia, Sen Nagai in Japan and Betty Heimann in the Indian view of the world. Sen Nagai also describes the constitution of the Japanese. The remaining contributions are: H. Schulte, the psychology of the sport and constitution; R. Allers, medical characterology, and K. Birnbaum, the problem of biophysics in constitution.

THE MEDICAL MUSEUM, MODERN DEVELOPMENT, ORGANIZATION AND TECHNICAL METHODS BASED ON A NEW SYSTEM OF VISUAL TEACHING. By S. H. DAUKES, O.B.E., M.D., D.P.H., D.T.M. and H., Director of the Wellcome Museum of Medical Sciences. Pp. 172, with 44 illustrations. London: The Wellcome Foundation, Ltd., 1929.

This volume is an interesting and important contribution to medical museology. A comprehensive system of linking various departments in medicine in synoptical demonstrations of great educational value is described in detail. The time has come when the medical museum must expand from being merely a collection of pathologic specimens into a living, progressive representation of medical knowledge and methods. This is the plan followed by the Wellcome Museum of Medical Science in London, and practically all of the forty-four full page illustrations in the book illustrate the exhibits and methods of that museum. The first chapter deals with the need of expanding the medical museum so that it may represent the growth of medicine as a whole; and the functions of the museum in this wider outlook in collecting and preserving material, in research and in education are set forth clearly and enthusiastically. By education in this connection is meant not only specific medical education but also the education of the public

in matters of health and hygiene. In chapter 2 the evolution of the system of the Wellcome Museum is outlined. Chapter 3 is concerned with the general arrangement, classification, sequence and grouping of specimens and exhibits. The succeeding five chapters deal with exhibits illustrating individual diseases under etiology, pathologic anatomy, symptomatology, treatment and prevention. These chapters will be of much service to persons in charge of growing museums of larger scope than just preserving and exhibiting pathologic specimens. Curators of such collections, however, will find much of interest and help in these chapters, particularly in chapter 5, which discusses the grouping, collection, preparation, etc., of pathologic material. In chapter 9 the possible objections to the synoptical method of demonstration are analyzed and answered. The last chapter discusses the museum of the future. "A museum lives more by what it gives than by what it receives"—in other words, the museum should not be treated merely as a depository of material but as an integrating and living influence in teaching medical knowledge. In several appendixes various problems of museum arrangement and methods are discussed with particular reference to carrying out the synoptical scheme. Finally come lists of references to museum methods. The book will be a helpful and stimulating guide to all who are concerned in developing progressive medical museums.

TULARAEMIA: HISTORY, PATHOLOGY, DIAGNOSIS AND TREATMENT. By WALKER M. SIMPSON, M.D., Director of Diagnosic Laboratories, Miama Valley Hospital, Dayton, Ohio. Price, $5.00. Pp. 162, with 53 illustrations and 2 color plates. New York: Paul B. Hoeber, Inc., 1929.

The growth of knowledge of tularemia is one of the most romantic chapters in the recent history of medical research. The first case in a human being was recognized by Wherry in 1912. In 1920 the term "tularemia" could not be found in the medical literature, and up until 1924 only 15 cases had been reported. During the next four years (1924-1928) over 800 cases were recognized in the United States, a large number of which were studied in the Hygienic Laboratory of the U. S. Public Health Service. The work of George W. McCoy, who discovered the organism of tularemia, and of Edward Francis, both of the U. S. Public Health Service, constitutes the foundation of our knowledge in this "new disease." In 1925 it was recognized by O'Hara in Japan, and in 1928 by Russian workers in the province of Astrakhan. Dr. Simpson has written an interesting and timely book on this disease. Here under one cover is a complete and accurate account of the history, distribution, clinical manifestations, pathology, bacteriology, diagnosis and treatment of tularemia. The author has emphasized certain features; namely, (1) the certainty of infection of laboratory workers; (2) the persistence of agglutinins in the blood of long recovered patients; (3) the cross agglutination of *Bacterium abortus* and *Bacterium tularense;* (4) the granulomatous character of the lesions in man as contrasted with the lesions in animals; (5) the cystine requirements of the organism in culture mediums; (6) its pleomorphism; (7) its penetration of the unbroken skin; (8) its invasion of fixed tissue cells; (9) its transmission through the egg of the tick to the next generation of ticks; (10) the great variety of insect hosts; (11) the great variety of animal hosts. There is a complete bibliography.

THE BLOOD PICTURE AND ITS CLINICAL SIGNIFICANCE (INCLUDING TROPICAL DISEASES). A GUIDEBOOK ON THE MICROSCOPY OF THE BLOOD. By PROFESSOR DR. VICTOR SCHILLING, Physician-in-Chief, the First Medical University Clinic, Charité, Berlin. Translated and edited by R. B. H. GRADWOHL, Director of the Pasteur Institute of St. Louis, and the Gradwohl School of Laboratory Technique. Seventh and eighth revised edition. Price, $10.00. Pp. 408, with 44 illustrations and 4 color plates. St. Louis: C. V. Mosby Company, 1929.

The first edition of this book was published in 1912. To this edition have been added sections on the typing of blood, the "guttadiaphot method," a discussion of Arneth's "Qualitative Blood Theory," the Bastonella group of Verruca peruviana.

The discussion of sedimentation of red corpuscles has been enlarged. Part 1 deals with technical matters. Here one notes that some of the methods would be difficult to carry out in the United States because the stain required or the particular instrument is not readily available. It is a disadvantage, too, that the chart for differential leukocyte count, on page 55, is reproduced with German designations. "Guttadiaphot" means a drop of blood viewed by transmitted light; the test appears to need special paper available in Germany. Part 2 deals with theory, morphology and division of the blood picture, and Part 3 with the fundamental principles for clinical use of the blood picture. The blood picture includes the erythrocyte picture as seen in smear and thick drop, the differential leukocyte picture in smear, the total number of leukocytes as determined by estimation or count, the number of red cells and the color index. Part 4 gives selected examples of the practical use of blood pictures or hemograms. There is a disease index with brief blood pictures, as well as a general index. The bibliography gives references chiefly to the German literature and there are no references to literature in the English language. There seems to be no reference in the book to sickle-cell anemia. The translator, who has done his work faithfully, expresses his belief that Schilling's book represents a marked advance in morphologic hematology and that it will be of great advantage to learn his methods.

THE DEVELOPMENT AND GROWTH OF THE EXTERNAL DIMENSIONS OF THE HUMAN BODY IN THE FETAL PERIOD. By RICHARD E. SCAMMON, Professor of Anatomy in the University of Minnesota, and LEROY A. CALKIN, Professor of Gynecology and Obstetrics in the University of Kansas. Price, $10.00. Pp. 367. Minneapolis: The University of Minnesota Press, 1929.

This is a monographic presentation of a noteworthy, quantitative study of fetal growth. "It consists of an account of the changes in the dimensions and external proportions of the body as determined from a large number of original observations and from a colligation of all available published data by other investigators. These data have been treated analytically, studied for the effects of various important artifacts on them, and are presented, in condensed tabular, graphic and analytic forms." The original data were obtained by about 35,000 measurements of 71 external dimensions of upward of 400 selected human fetuses ranging from 2.3 to 54.4 cm. in crown-heel length. Measurements were made also on 33 living newborn infants, but the data on these are not included in the final tabulations. Following a detailed statement of the general plan of the investigation are given: the summaries of the measurements, a general discussion and a general summary. There is an extended bibliography, 180 tables, 73 figures, and 70 field graphs. In the preface by Prof. C. M. Jackson it is pointed out that the main outcome of this impressive work is a new principle, namely, that "in general the linear growth of the various parts of the body is in uniform ratio during the fetal period." Any changes in proportion during this period appear to arise from irregularities established in the earlier, embryonic period. The work of the publisher is appropriate and commendable. This monogaph will be an essential source of reference to students of the problems of growth.

THE ADRENALS, THEIR PHYSIOLOGY, PATHOLOGY AND DISEASES. By MAX A. GOLDZIEHER, Former Professor of Pathology, University of Budapest; Director of Laboratories, United Israel Zion Hospital, Brooklyn. Pp. 436, with 73 text-figures. New York: The Macmillan Company, 1929.

The purpose of this book is to summarize the present knowledge concerning the suprarenals, their structure, physiology and diseases. It represents apparently an expansion of an earlier monograph by the author which was based on his own experimental and anatomic studies. There are six chapters, which deal with the following subjects: development, anatomy, physiology, pathologic anatomy, pathologic physiology and suprarenal organotherapy. The longest chapters are the two dealing with pathologic anatomy and physiology of the suprarenals. There are

seventy-three text-figures, most of them illustrating the microscopic appearances of morbid changes in the suprarenals. Unfortunately for some reason many of the figures are so indistinct as to be worthless. There is an extensive bibliography, covering more than 100 pages. The references are given under topics in alphabetical order according to authors' names. The various topics are not located easily without first consulting the index in which the bibliography is referred to by pages under the main subjects. The use of special abbreviations of the names of periodicals, requiring a key, seems to be an unnecessary complication that could have been avoided by following the standard style of abbreviations of the *Quarterly Cumulative Index Medicus*. The style is not consistently clear and direct. The book contains a large amount of information about the suprarenals and their many and difficult problems. It will be of value as a base for sources to the student of the suprarenal gland.

SELECTED READINGS IN PATHOLOGY FROM HIPPOCRATES TO VIRCHOW. Edited by ESMOND R. LONG, Professor of Pathology in the University of Chicago. Price, $4. Pp. 301. Springfield, Ill.: Charles C. Thomas, 1929.

The volume contains a set of excerpts (English) from medical classics of particular significance to the study of pathology as commonly understood. Some of these excerpts mark milestones in the development of knowledge of disease, while others are samples of writings that have had exceptional influence. The time covered extends to the publication in 1863 of the translation by Frank Chance of Virchow's Cellularpathologie, that is, roughly to the beginning of the microbic era. It is the gradual replacement of "humoral" by "cellular" pathology that is illustrated by the book; infection and immunity do not come within its scope. Thirty-six masters are represented, and of these, three are American — Horner, Gerhard, Gross. The order in which the excerpts come is chronologic. Each excerpt is preceded by a brief but illuminating characterization of the work of the author by the editor. There are twenty-five illustrations, mostly of authors themselves. The work of the publisher merits a word of commendation. There is now available in attractive form a well selected and representative set of documents, all in English and of convenient length, illustrating the development of pathology. Many of the works from which excerpts are taken are often quoted, especially in the courses on pathology, but for various reasons only seldom, very seldom read. Long's Readings makes it easy to form a more intimate acquaintance with these classic writings, and supplements well his excellent History of Pathology.

BLOOD GROUPING IN RELATION TO CLINICAL AND LEGAL MEDICINE. By LAURENCE H. SNYDER, D.Sc., Associate Professor of Zoology, North Carolina State College, Raleigh; Committee on Blood Grouping, National Research Council. Price, $5.00. Pp. 153, with 28 illustrations and 5 plates. Baltimore: Williams & Wilkins Company, 1929.

Snyder's book is the first comprehensive American book on the theory and practice of blood grouping. The author is in the field of his special competence, as he is an active worker on grouping problems particularly as they touch genetics and physiology. Fortunately he is experienced also in practical transfusion, which is discussed in considerable detail. The book may be divided as follows: the principles of isohemagglutination; transfusion—history, indications, technic of blood testing; methods; blood groups in legal medicine and in pathology; blood groups in animals; racial distribution of blood groups and its anthropologic significance. In other words, the trends of interest in, and the practical applications of, blood grouping are considered. There is an extensive bibliography. The materials are handled adequately and the style is clear and direct. The book will be useful for all who are interested in blood grouping.

Books Received

REPORT OF THE HAFFKINE INSTITUTE FOR THE YEAR 1928. By Major S. S. Sokhey, I.M.S., Officiating Director, Haffkine Institute. Price, 2 annas or 3 pence. Pp. 43. Bombay: Government Central Press, 1929.

INFECTIOUS DISEASES AND OTHER FEVERS IN INDIA: A MANUAL FOR STUDENTS AND PRACTITIONERS. By Purshotamdas T. Patel, M.D. (London), M.R.C.P. (London), D.T.M. & H. (Cantab.), F.C.P.S. (Bombay), Medical Superintendent, City Isolation Hospitals (Arthur Road) and Maratha Plague Hospital, Hon. Physician, King Edward VII Memorial Hospital and Turner Sanatorium for Tuberculosis, Clinical Professor of Infectious Diseases, Medical Colleges, Bombay. Calcutta and London: Butterworth & Company, Ltd., 1929.

A SURVEY OF THE LAW CONCERNING DEAD HUMAN BODIES. By George H. Weinmann. Bulletin 73 of the National Research Council. Issued under the Auspices of the Committee on Medicolegal Problems, National Research Council. Price, $2. Pp. 199. Washington, D. C.: National Research Council, 1929.

EPIDEMIC ENCEPHALITIS: ETIOLOGY, EPIDEMIOLOGY, TREATMENT. Report of a Survey by the Matheson Commission: William Darrach, chairman; Haven Emerson, Frederick P. Gay, William H. Park, Charles R. Stockard, Frederick Tilney, Willis D. Wood, Hubert S. Howe, secretary, Josephine B. Neal, director of survey, and Helen Harrington, epidemiologist. Price, $3. Pp. 849, including bibliography and author and subject indexes. New York: Columbia University Press, 1929.

THE IMMUNOLOGY OF PARASITIC INFECTIONS. By William H. Taliaferro, Ph.D., Professor of Parasitology, the University of Chicago. Price, $6. Pp. 414. New York: Century Company, 1929.

MEDICAL LEADERS FROM HIPPOCRATES TO OSLER. By Samuel W. Lambert, M.D., and George M. Goodwin, M.C. Price, $5. Pp. 331, with 32 illustrations. Indianapolis: Bobbs-Merrill Company, 1929.

THE RIGHT HONOURABLE SIR THOMAS CLIFFORD ALLBUTT, K.C.B., M.A., M.D., F.R.C.P., F.R.S., Hon. M.D., D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge; Fellow and Sometime Classical Scholar of Gonville and Caius College: A Memoir. By Sir Humphry Davy Rolleston, Bart., G.C.V.O., K.C.B., M.A., M.D., Hon. M.D., D.Sc. D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, Somtime President of the Royal College of Physicians of London. Price, $6. Pp. 314. New York: The Macmillan Company, 1929.

DISEASES TRANSMITTED FROM ANIMALS TO MAN. By Thomas G. Hull, Chief Bacteriologist, Illinois Department of Public Health; Assistant Professor of Pathology and Bacteriology, University of Illinois, College of Medicine. With an Introduction by Veranus A. Moore, Director, New York State Veterinary College, Cornell University. Price, $5.50. Pp. 352, with 29 illustrations, 43 tables and index. Springfield, Ill.: Charles C. Thomas, 1930.